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Original Communications

INTERPRETATION OF BUNDLE-BRANCH BLOCK BY MEANS OF THE MONOCARDIOGRAM*

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THE diagnostic distinction between right and left bundle-branch block in human beings is still uncertain. Lewis and his co-workers have attempted to apply their experimental work on animals to the diagnosis of human bundle-branch block, but their conclusions have been at variance with much clinical and pathological evidence and have failed of general acceptance.

This paper is an attempt to show that, by means of a method of analysis previously described,[1] it is possible to determine right and left bundle-branch block in a manner which is consonant with the clinical, experimental and pathological findings. This method of analysis is based on the fact that the three separate leads of the electrocardiogram are merely a conventional method of recording one single series of electrical phenomena. The heart itself does not produce the three separate cardiographic curves which we designate Leads I, II and III, but these curves are derived from a single series of phenomena and constitute a conventional and convenient method of observing and recording these phenomena. W. Einthoven[2] and many others have recognized this and have discussed the significance of the threefold electrocardiogram.

It is readily understandable that the ordinary electrocardiogram which is spread out on a time axis is admirably adapted to the portrayal and analysis of cardiac arrhythmias because time relations play an important part in such analyses. On the other hand the determination of the site of anatomical, physiological and pathological changes in the heart has been difficult because of the unsuitability of the ordinary electrocardiogram to this end. The curves could be made much better suited to the delineation of these spatial relationships if instead of spreading them out on a time axis (and thereby sacrificing spatial

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relationships) we could spread them out spatially (thereby neglecting the time relationship).

A way of doing this was worked out mathematically by Einthoven, Fahr and deWaart,[3] but it has proved to be a very difficult and cumbersome method. In 1916 an encounter with the difficulties of this method led me to devise a method of analyzing the electrocardiogram[1] which gave instead of three leads a single curve or monocardiogram, the axes of which had a spatial significance. This monocardiogram is really a fusion of the three leads of the electrocardiogram into a single curve by an algebraic reversal of the process by which three leads are obtained from one heart. The derivation of this single curve

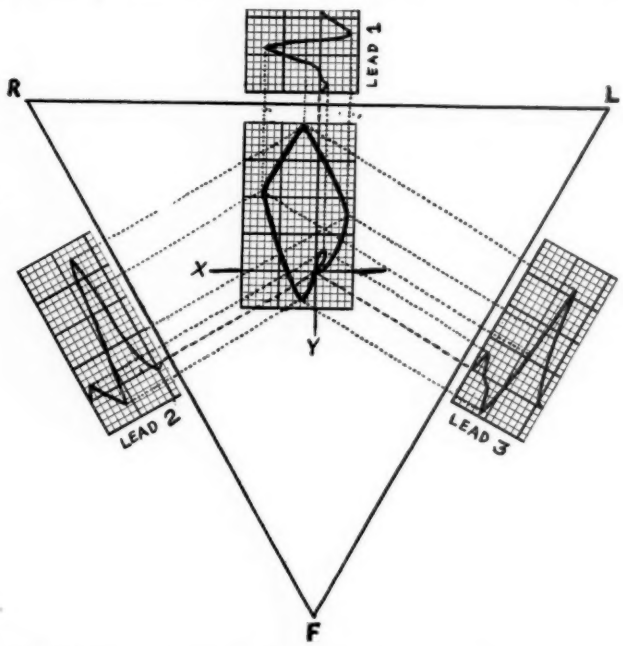

Fig. 1.—This shows the monocardiogram which is derived from an electrocardiogram published by Einthoven[4]. It can be seen that the three leads of the electrocardiogram are really derivatives of the monocardiogram, obtained by successive projections of the monocardiogram on the three sides of the equilateral triangle.

Note that in this monocardiogram, as in all others shown in this article, the right side is on the observer's left. This is in accordance with the ordinary usage in regard to Einthoven's triangle and facilitates interpretation.

or monocardiogram was at first purely theoretical and mathematical, but in 1925 I succeeded in devising an experimental apparatus* for obtaining and recording this monocardiogram directly from the patient, thereby adding further proof of the validity of the method.

The method of deriving such a single curve or monocardiogram can be made clear by reference to Fig. 1. This illustration shows the main deflection in the three leads of an electrocardiogram originally pub-

*This apparatus, called a monocardiograph, was developed with the aid of a grant from the Rockefeller Institute and a description of it will soon appear.

lished by Einthoven.[4] These three leads are here shown arranged parallel to the sides of an equilateral triangle in such a way that the projections of the three base lines meet at the center of the triangle. Under these conditions the projections of simultaneous instants of the three leads meet at points which, taken successively, constitute a single curve or monocardiogram. The reasons why this particular construction is adopted are made clear in my original paper (q.v.) and depend on the fact, as elucidated by Einthoven, that the projections on the sides of an equilateral triangle of any straight line drawn within the triangle have a relationship similar to the relationship existing between the leads of an electrocardiogram.

The production of a single curve from the three leads of an electrocardiogram is more than a mathematical or geometrical *tour de force.* Fig. 1 provides a clear and comprehensive diagram of the manner in which three leads are derived from the single series of electrical phenomena taking place in the heart. The central curve or monocardiogram represents graphically the electrical phenomena which occur during successive instants (hundredths of a second) throughout the duration of the main deflection, while the three leads can be considered as merely the projections of this central curve on the three sides of a triangle. They are really like three shadows of the central curve, thrown in three different directions.

But while the shadows are spread out in time the central curve is spread out in space. When this curve is to the right and above the zero point, it indicates that the center of negativity* is to the right and above the electrical center† of the heart. When the curve moves to the left of the zero point it indicates that the center of negativity in the heart has shifted to the left. Thus the monocardiogram affords us a method of localizing in a plane various parts of the cardiac musculature, of analyzing an electrocardiogram with regard to its anatomical significance, of determining what part of the cardiac musculature is responsible for various types of bizarre and abnormal electrocardiograms, of locating the site of origin of extrasystoles, etc.

A consideration of the method of analysis here outlined will make plain that every properly taken electrocardiogram carries in itself the possibility of being reduced to a single curve or monocardiogram and that this single curve can make evident a number of hitherto concealed anatomical and spatial relationships. Numerous questions as to the site and extent of myocardial damage following acute coronary artery

*Center of negativity is defined in the original description of the monocardiogram as follows: "If at any moment there are present in the heart several (negative) electrical charges which have value (intensity, voltage) and position (direction) then the center of negativity is that point which represents the algebraic sum of all the potential differences."

†The electrical center of the heart is the point which is represented by the center of the equilateral triangle. It may be defined as that point at which an electrical charge will produce no deflection in any lead of the electrocardiogram.

occlusion can be answered by means of this method of analysis. The determination of the site and extent of the lesions which produce electrocardiographic changes of the type known as intraventricular conduction defect or arborization block can be studied by this method. The exact nature of fibrillation and flutter and the location of the circus stimulation in flutter can be studied. The nature and significance of ventricular preponderance and its relationship to ventricular hypertrophy and to changes of position of the heart can be made clear.

Much of my previous study has been based upon monocardiograms derived from electrocardiograms. Such curves, however, are open to

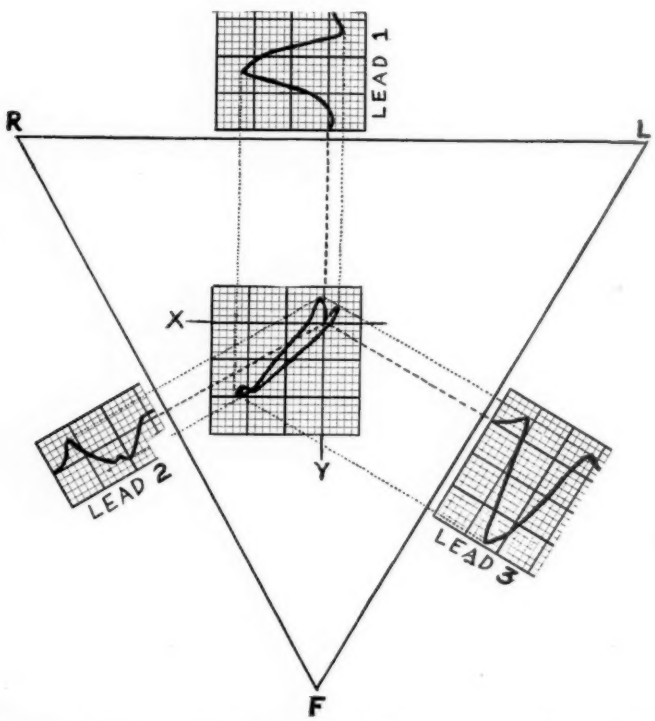

Fig. 2.—This shows the monocardiogram derived from an electrocardiogram published by Lewis (Clinical Electrocardiography, London, 1913, p. 31). Note that in this illustration the monocardiogram is mainly to the right (the observer's left) of the zero point while in Fig. 3 the curve is mainly to the left (the observer's right) of the zero point.

the criticism that they are theoretical and artificial and have no real basis in fact. The development of an instrument by means of which the monocardiogram can be recorded directly from a patient without the necessity for any intermediate electrocardiogram has removed these objections.

Much of the theoretical work of the past ten years must be supplemented with actual graphic records before our material is ready for publication but in the matter of bundle-branch block the curves are

so obvious and unequivocal that their analysis does not involve any appreciable doubt.

Inasmuch as most of the confusion about bundle-branch block has arisen from the work of Sir Thomas Lewis I have taken as typical instances of bundle-branch block the two curves which he published in his textbook, *Clinical Electrocardiography* (London, 1913, page 31). These curves are similar to present-day curves except that time intervals are indicated in thirtieths of a second. Each of these curves has been analyzed in a manner similar to that illustrated by Fig. 1, and the resulting monocardiograms are presented in Figs. 2 and 3.

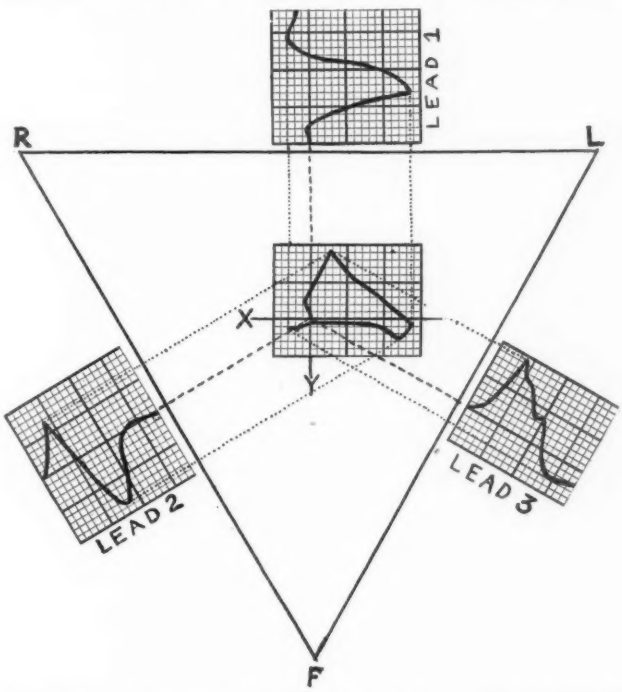

Fig. 3.—This shows the monocardiogram derived from an electrocardiogram published by Lewis (Clinical Electrocardiography, London, 1913, p. 31). Note that this monocardiogram is mainly to the left (the observer's right) of the zero point.

It can be seen at once that these two monocardiograms differ considerably from the normal as represented in Fig. 1. In Fig. 2 which is derived from an electrocardiogram which, according to Lewis indicates "functional defect of the right division of the auriculo-ventricular bundle," the monocardiogram shows a shift of the center of negativity downward and to the *right*. In Fig. 3, derived from an electrocardiogram which, according to Lewis, indicates "functional defect of the left division of the auriculo-ventricular bundle," the monocardiogram shows a shift of the center of negativity to the *left*.

That this shifting of the center of negativity in bundle-branch block is a constant phenomenon is shown by Figs. 4 and 5 which show the

monocardiograms of two instances of bundle-branch block which were recorded in the cardiographic laboratory of Mount Sinai Hospital. The same obvious shifting of the center of negativity is shown: one to the right and the other to the left.

Now it is practically self-evident that in the human heart any delay or block in the excitation of the left ventricle will result in a shifting of the center of negativity toward the right and that, conversely, a delay or block in the excitation of the right ventricle will shift the center of negativity toward the left side. It is also obvious that in right bundle-branch block the excitation of the right ventricle is de-

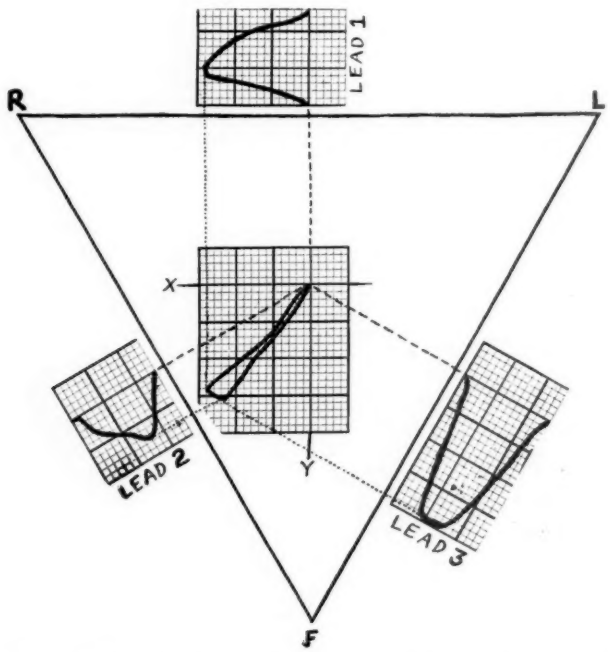

Fig. 4.—Monocardiogram of a case of bundle-branch block observed in the Mount Sinai Hospital. Observe the general resemblance to Fig. 2. The original electrocardiogram is shown in Fig. 7-*A*.

layed and that in left bundle-branch block the excitation of the left ventricle is delayed. The analysis of such curves by the monocardiogram shows clearly that in right bundle-branch block the electrocardiogram shows an inverted main deflection in Lead I while in left bundle-branch block the main deflection is upright in Lead I.

The criteria then for bundle-branch block may be defined thus:

Electrocardiograms which indicate bundle-branch block exhibit the following characteristics:

1. A main deflection which shows a width of at least twelve hundredths of a second, good amplitude and smooth contour.

2. A T-wave which is opposite in direction to the main deflection and which is practically a continuation of the main deflection without any definite iso-electric transition period.
3. Right bundle-branch block is indicated by an inverted main deflection in Lead I and an upright main deflection in Lead III.
4. Left bundle-branch block is indicated by an upright main deflection in Lead I and an inverted main deflection in Lead III.

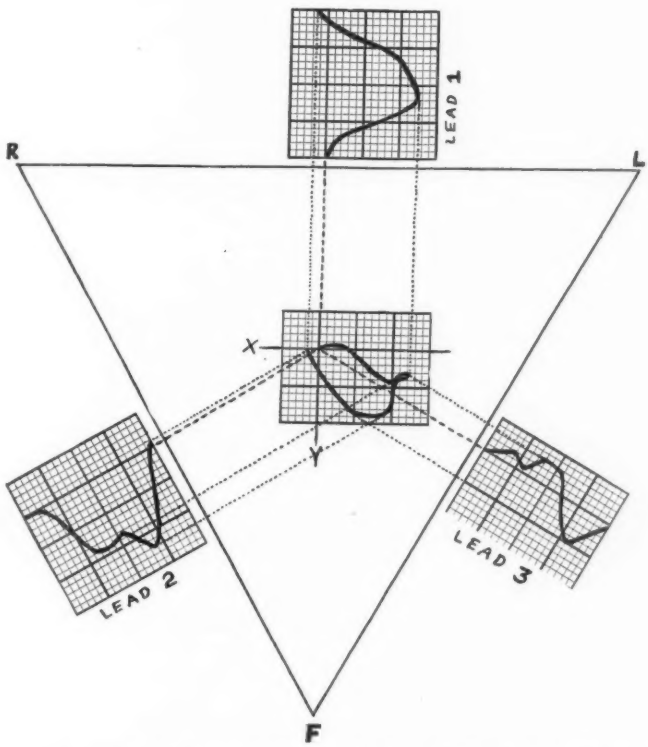

Fig. 5.—Monocardiogram of a case of bundle-branch block observed in the Mount Sinai Hospital. Observe the general resemblance to Fig. 3. The original electrocardiogram is shown in Fig. 7-*B*.

Points 1 and 2 summarize the generally accepted characteristics of bundle-branch block. Points 3 and 4 summarize our interpretation of right and left bundle-branch block and their differentiation.

It is not the purpose of this paper to discuss critically all the evidence in favor of this interpretation. It will suffice here to mention that left bundle-branch block occurs more than ten times as frequently as right bundle-branch block, which is in accord with the fact that post-mortem examination usually reveals localization of the myocardial damage in the left ventricular musculature. To any one who has seen instances of the gradual evolution of electrocardiograms from

fairly normal to the type characteristic of intraventricular conduction defect and then toward the type which is characteristic of left bundle-branch block it seems quite superfluous to point out that the progressive injury is practically always located on the left side.

As this paper was approaching completion a very apt illustrative case presented itself. The patient, a man of sixty years, evidently extremely ill, had an electrocardiogram which we regard as characteristic left bundle-branch block. The monocardiogram shown in Fig. 6 is like Fig. 2 and Fig. 4. Post-mortem examination revealed an

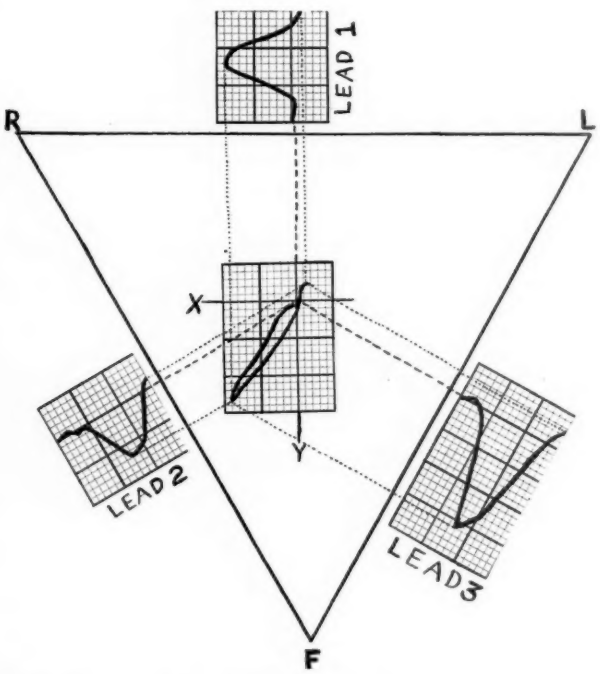

Fig. 6.—Monocardiogram of a case of bundle-branch block observed in the Mount Sinai Hospital. Observe the general resemblance to Figs. 2 and 4. The original electrocardiogram is shown in Fig. 7-*C*.

enormous organized thrombus adherent to the left septum and the anterior wall of the left ventricle with extensive destruction and fibrosis of the myocardium of the left side of the septum and the anterior wall of the left ventricle. There was narrowing of the left coronary artery at its origin. There was a relatively tiny thrombus at the very apex of the right ventricle with no extensive gross damage to the right ventricular musculature.

The coincidence of extensive destruction in the region of the left bundle branch with a definite ante-mortem diagnosis of left bundle-branch block was striking. Were it the only instance in which such a

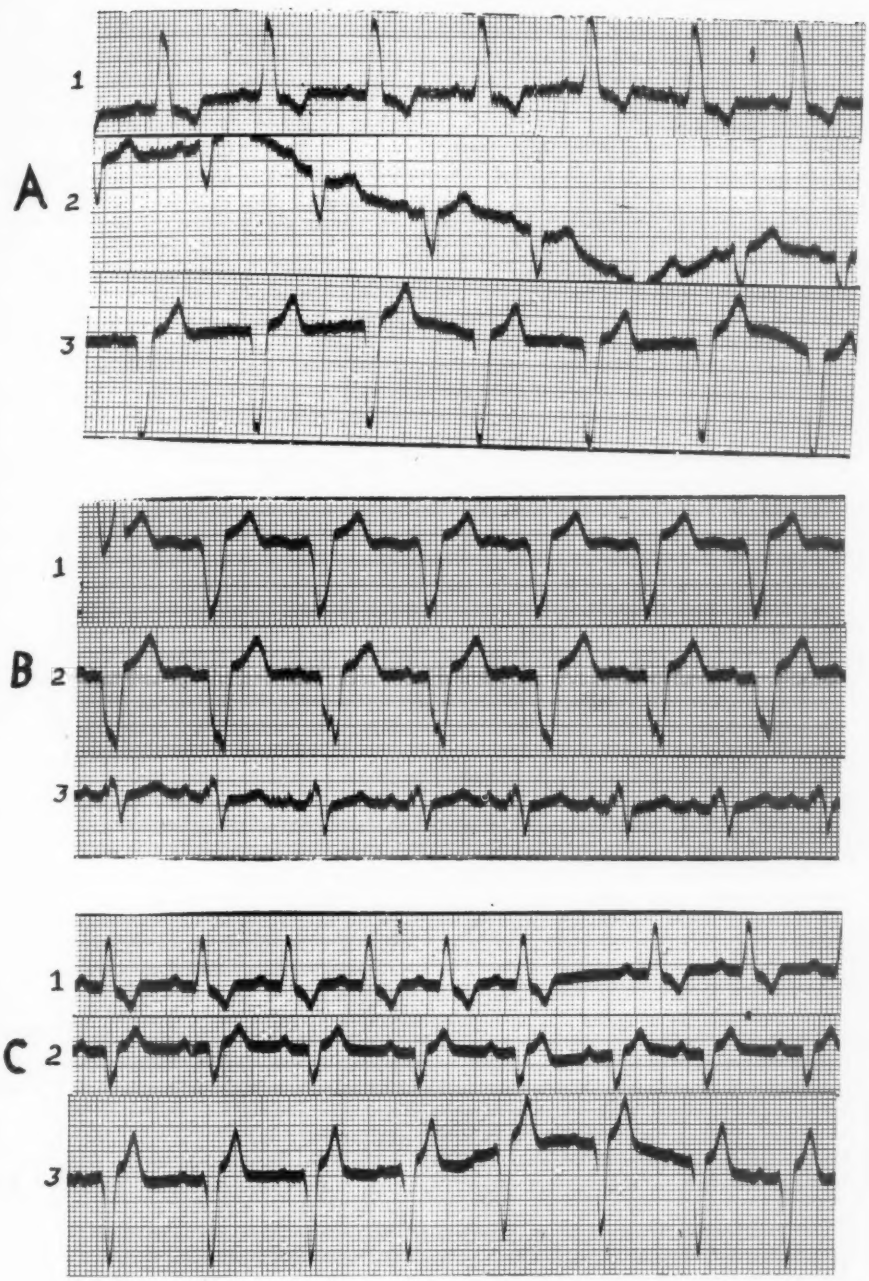

Fig. 7.—*A*, Electrocardiogram from which monocardiogram shown in Fig. 4 was derived. *B*, Electrocardiogram from which monocardiogram shown in Fig. 5 was derived. *C*, Electrocardiogram from which monocardiogram shown in Fig. 6 was derived.

coincidence was observed it could hardly be regarded as convincing evidence. But we have repeatedly seen the association of this type of electrocardiogram with a gross lesion involving exclusively the left ventricle. The service of any large active hospital will provide numerous similar cases.

As to the reasons for the earlier errors in the interpretation of right and left bundle-branch block it should be pointed out that the conclusions derived from experiments on the canine heart should not be applied to the human heart without taking into consideration the marked differences between canine and human hearts in regard to both the position of the anatomical axes and the angle of the interventricular septa. In the experimental work performed on a rhesus monkey and reported by Lewis[5] the monkey's normal electrocardiogram shows a decided tendency toward right ventricular preponderance, a condition which tends to invalidate the applicability of the results to the human heart.

As early as 1916 the question of right and left bundle-branch block was a moot one. By 1917 these monocardiographic studies, supported by their correlation with numerous post-mortem observations, seemed sufficiently conclusive to justify routinely reporting the localization of bundle-branch block in a manner opposite to the published interpretation of Lewis. Within the past ten years and especially within the past few years numerous writers have dissented from the "orthodox" interpretation. The experience which we have derived from the monocardiogram since its employment in 1917 is now adequate to warrant publication in the hope that the weight of evidence, experimental, clinical, anatomical and statistical, will soon succeed in bringing the general interpretation of bundle-branch block into agreement with the facts. Old errors cling stubbornly and it is at times necessary to remind ourselves that while truth may be a bitter pill it is a good physic.

SUMMARY

1. The article describes a method of analyzing the electrocardiogram by a fusion of the three leads into a single curve or monocardiogram.

2. This method of analysis brings out anatomical and spatial relationships hitherto concealed and facilitates the investigation of such problems as the site and extent of myocardial and coronary lesions, the nature of fibrillation and flutter and the sites of origin of extrasystoles.

3. It is peculiarly well adapted to the diagnosis of right and left bundle-branch block.

4. Numerous applications of this method of analysis show that in right bundle-branch block the electrocardiogram has an inverted main

deflection in Lead I while in left bundle-branch block the main deflection is upright in Lead I.

5. The reasons for previous misinterpretations are discussed briefly.

The writer wishes to acknowledge his indebtedness to Dr. M. A. Rothschild and Dr. George Baehr for their suggestions and encouragement in the preparation of this paper.

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THE EFFECTS OF DIGITALIS ON PREMATURE AURICULAR CONTRACTIONS ASSOCIATED WITH ATTACKS OF PAROXYSMAL AURICULAR FIBRILLATION. THE USE OF THE DRUG IN THE TREATMENT AND PREVENTION OF CERTAIN FORMS OF THESE ARRHYTHMIAS*

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INTRODUCTION

AURICULAR fibrillation, ushered in with a very rapid ventricular rate varying between 150 and 250 beats per minute and not slowing with rest, is one of the most severe forms of this type of irregularity in patients with established heart disease and signs of congestive heart failure. It is one of the few disturbances of the cardiac mechanism which, if left untreated, may result in symptoms and signs grave enough to cause death within a comparatively short time after its onset.

Within the last few years there have been admitted to the wards of the Montefiore Hospital a group of seven such patients with advanced organic heart disease and signs of congestive heart failure who have been subject to frequent attacks of auricular fibrillation with a persistently high ventricular rate. These attacks were invariably preceded for from one to three days by premature auricular contractions first coming on singly, then in groups of two or more. From prolonged observation of these patients under controlled conditions and a variety of experiments carried out on them it has been noted that almost all showed restoration to normal sinus rhythm when they were given single large doses of digitalis within a comparatively short time after the auricular fibrillation was recognized. In all of these instances, the administration of adequate and judicious doses of digitalis during their periods of normal sinus rhythm could prevent the onset of the premature auricular beats, and prevent the appearance of auricular fibrillation. Even after the premature auricular beats set in, it was possible to abolish them and to restore sinus rhythm with digitalis. In every instance a relatively slow sinus rate could be maintained after normal rhythm had been established by the effective use of digitalis.

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Because of the close relationship that exists between the administration of digitalis and the restoration of normal sinus rhythm following the onset of premature auricular beats as well as between the use of digitalis and the prevention of recurrences of auricular fibrillation, with the accompanying signs of severe congestive heart failure, these patients form a distinct group among the large number of subjects with auricular fibrillation and from the point of view of treatment should be given special consideration.

Three of these cases are reported in detail in order to call attention to the characteristic sequence of events that takes place following the onset of these irregularities and their response to variable dosages of digitalis.

REPORT OF CASES

CASE 1.—S. J., a female, aged 30 years, was admitted to the Montefiore Hospital on Aug. 6, 1927. Her chief complaints were shortness of breath, precordial distress, weakness and swelling of the lower extremities.

Previous Illness.—She suffered her first attack of rheumatism at the age of 20 years. At 24, she was informed that she had heart trouble. Seven years ago (January, 1923) the patient began to notice for the first time that emotional disturbances upset her a great deal. Following a quarrel or a crying spell and at times shortly after least exertion she would become conscious of her heart beating very rapidly.

At first she would feel isolated thumps of her heart against her chest wall. Within one to two hours she would be conscious of their increase in frequency. As she felt and counted her pulse and noticed that it increased in frequency and irregularity, she would find herself breathing with difficulty. At the height of an attack she began to feel precordial distress. At first the precordial pains were localized in the region of the left fifth intercostal space near the mid-clavicular line, but as the attack increased in severity, the pains radiated to the left shoulder and to the inner side of the left arm, and finally she felt the pains in the smaller fingers of the left hand.

Nothing would relieve her pains or the shortness of breath except the adequate administration of digitalis. (These were the patient's own observations.) She could predict almost with regularity when the attacks would cease by the way she responded to this particular drug. With the slowing of the heart rate she would begin to lose her precordial distress, her breathing would become easier, and within one to three days she could again count her regular pulse rate if she had received a "strong dose of digitalis."

Physical examination on admission to the Montefiore Hospital revealed a poorly nourished female complaining of difficulty in breathing. There was intense cyanosis of the lips, cheeks and ears. The superficial vessels of the neck were markedly distended. The apical impulse of the heart was in the fifth intercostal space in the region of the midclavicular line. A short rough systolic murmur followed by a prolonged diastolic murmur could be heard as far down as the xiphoid region. The heart rhythm was totally irregular and averaged 120 beats per minute. There was a pulse deficit of an average of 30 beats per minute. The blood pressure was 145 mm. of mercury systolic and 60 mm. diastolic.

The lungs showed dullness with absent breath sounds over the right base posteriorly from the angle of the scapula to the base. Many moist râles were heard at the left base posteriorly. The liver edge was palpable 3 cm. below the costal margin. There was moderate swelling of the lower extremities.

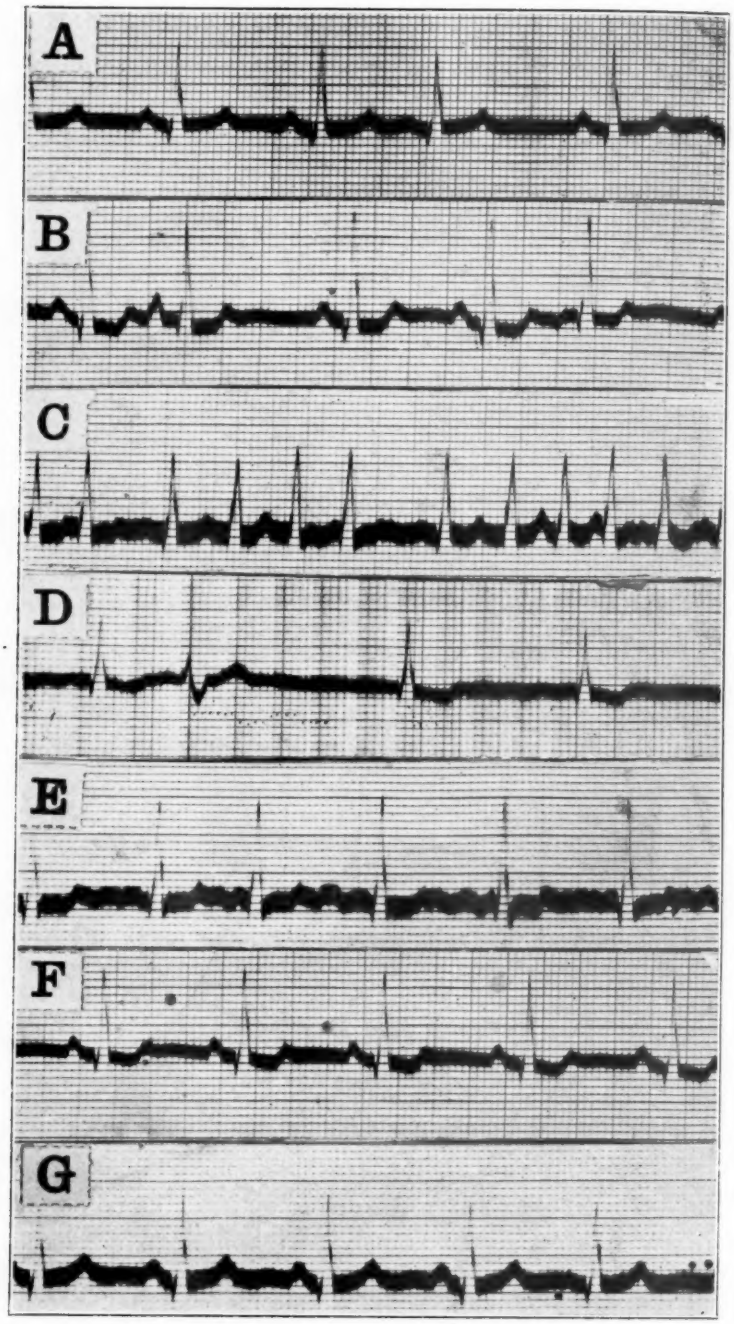

Fig. 1.—Case 1. A series of serial electrocardiograms, Lead I only, showing the appearance of successive changes in rhythm starting with (*A*) Sinus arrhythmia and premature auricular beats with an average ventricular rate of 100 beats per minute; (*B*) bigeminal rhythm due to premature auricular beats with an average ventricular rate of 148 beats; (*C*) a seizure of paroxysmal auricular fibrillation with a rapid ventricular rate; (*D*) alternate premature ventricular beats and partial block following the daily use of 3 c.c. of digitalis for seven days after the onset of auricular fibrillation, showing the perpetuation of auricular fibrillation with small daily doses of digitalis; (*E*) auricular fibrillation with a ventricular rate of 75 beats per minute four days after the preceding record and after the withdrawal of digitalis; (*F*) restoration to normal sinus rhythm, record taken on same day as above; (*G*) fifteen days later, the beginning of another attack with the appearance of premature auricular beats.

Course and Progress.—On admission, the patient was put to bed and promptly given 3 c.c. of the tincture of digitalis to control her ventricular rate. Five days later a thoracentesis of the right chest yielded 1200 c.c. of clear straw colored fluid. With continued rest and further digitalization (3 c.c. daily) she felt better at the end of seven days. The edema of the legs disappeared, the liver edge was no longer palpable, she became free from dyspnea, and the heart rate had slowed to an average of 70 beats per minute. It was noticed, however, that at the end of nine days after she had received a total of 27 c.c. of the tincture of digitalis, she showed partial heart-block with a basic ventricular rate of 44 and bigeminal rhythm due to alternate premature ventricular beats of the ventricle. At this time all medication was discontinued.

An electrocardiogram taken on Sept. 12, 1927, about one month after her admission revealed the presence of sinus rhythm. This unusual sequence of events interested me very much, and the patient was watched from day to day and studied very carefully with the idea of determining, if possible, whether the return to sinus rhythm was spontaneous or whether it was actually due to the use of digitalis.

One month later (Oct. 12, 1927) following an exciting debate with her roommate, the patient began to complain of irregular heart action and shortness of breath. Examination on that day revealed coupled rhythm with irregular heart action averaging 120 beats, but without any pulse deficit. These extra beats came at times singly, at other times in groups of two, and once in every five minutes groups of three could be counted interrupting the basic rhythm.

Repeated electrocardiograms taken through the day revealed premature auricular beats but a basic sinus rhythm. This irregularity of the heart was allowed to persist for six hours, at the expiration of which time the patient was beginning to complain of shortness of breath and a tender but not markedly enlarged liver. The administration of a single dose of 15 c.c. of the tincture of digitalis relieved her within five hours of all of her symptoms. The premature auricular beats gradually disappeared. Her ventricular rate receded to 74 beats per minute, and on the following morning the heart rate was regular and averaged 54 beats. For the ensuing two weeks she was very comfortable and up and about most of the time.

On Oct. 25, 1927, at 3:40 P.M. the patient began to complain again of shortness of breath and irregular action of the heart. The onset was gradual and was preceded by isolated premature auricular beats as evidenced by the electrocardiograms. Most of these beats had a compensatory pause. One hour later the rhythm was distinctly coupled. The heart rate was 128 beats per minute but irregular. The patient began to breathe with difficulty. The face assumed an anxious expression. Large beads of perspiration appeared on the forehead. Two hours later the ventricular rate averaged 210 beats per minute. It was difficult to state with certainty that auricular fibrillation was present, for there was no pulse deficit. Four hours after the onset of this seizure the liver edge was palpable below the level of the umbilicus and it was painful and tender to touch.

A dose of 10 c.c. of the tincture of digitalis was administered to her at one time and within the next four hours her heart rate gradually came down to 70 beats per minute. It was regular on the following morning, but she still had some difficulty in breathing because during this seizure fluid had accumulated in the right pleural cavity. Three days later, she was up and about feeling well again.

Between Oct. 25, 1927, and Jan. 31, 1929, at which time the patient developed permanent auricular fibrillation, she was seen and studied during twelve paroxysmal seizures of these arrhythmias. Innumerable electrocardiograms taken preceding, during and subsequent to these attacks revealed a definite clinical and graphic sequence of events for each attack and these I wish to discuss.

Emotional disturbances were the principal precipitating factors. Each seizure would be ushered in with premature auricular beats at first coming on singly and then in groups of two and three. As these became more frequent the ventricular rate would approximate 150 beats per minute and be irregular. The administration of a large dose of digitalis given at this time would gradually slow the ventricular rate, the premature beats would disappear, the patient's symptoms of breathlessness would subside, and the arrhythmia would pass away without fibrillation of the auricles setting in. During the presence of sinus rhythm the appearance of premature auricular beats could almost invariably be prevented by the daily use of a sufficient quantity of the drug to maintain sinus slowing. As the effect of the drug would wear off, the whole sequence of events described above would repeat itself.

The administration of a small daily dose of digitalis during the presence of established auricular fibrillation would invariably perpetuate the auricular fibrillation and cause heart-block with multiple premature beats of the ventricle indicating the toxic effects of the drug. It was only during the effective exhibition of a large dose of digitalis at one time that the fibrillation would pass off.

The auricular fibrillation was allowed to continue for several days at a time in order to note the effects on the symptoms and signs. Each time this was done, after about three days, following the onset, dyspnea would become extreme, the liver edge would get large and tender, and pulmonary edema with swelling of the legs would become evident. The high ventricular rate persisted even after the use of large doses of opiates. The longest period during which this patient was allowed to maintain this high ventricular rate was seven days. At this time the administration of a 15 c.c. dose of digitalis at one time resulted after two days in the restoration of sinus rhythm. The symptoms of congestive heart failure following the onset of her irregularities cleared up within five days after the establishment of sinus rhythm.

Finally the auricular fibrillation was allowed to continue for a period of several days again, when the intravenous use of digitalis was instituted to determine whether the rhythm would return to normal more quickly by this method than by the oral administration. Nine c.c. of digifolin were given to her at one time intravenously. The heart rate slowed two hours later which was about two hours sooner than when the drug was given orally, but the return to normal sinus rhythm did not take place until two days after that.

Permanent auricular fibrillation set in on Jan. 31, 1929, and shortly afterwards the patient died in severe congestive heart failure.

CASE 2.—C. K., a female, aged 59 years, was admitted to the Montefiore Hospital on Aug. 8, 1928. Her chief complaints were shortness of breath on exertion and recurrent attacks of severe palpitation of the heart. These symptoms were of approximately two years' duration.

Previous Illness.—The patient had been well until five years ago (June, 1925) when during convalescence from pneumonia she began to notice, for the first time, breathlessness on exertion.

In the winter of 1927 she experienced fainting sensation, following excitement and exertion such as scrubbing floors or walking up a flight of stairs. On rest and "medication" she overcame these difficulties, but there were recurrences of symptoms in March, 1928. In April, 1928, a severe attack of vomiting in addition to her other complaints compelled her to seek admission to the People's Hospital where she remained for three weeks and improved considerably under rest and medication. She had been at home since her discharge from that hospital.

Physical examination on admission to the Montefiore Hospital revealed a fairly nourished woman, severely dyspneic, with marked cyanosis of the face, lips, ears and hands. There was distention of the superficial vessels of the neck. Her chest

was barrel shaped. The apical impulse of the heart was not palpable, and percussion of the cardiac outlines was unsatisfactory. The heart sounds were of poor quality. The rhythm was totally irregular and averaged 182 beats per minute. There was a pulse deficit of 32 beats. The blood pressure was 180 mm. of mercury systolic and 120 mm. diastolic. There was dullness at the left base posteriorly with many moist râles that were heard all over the chest as far up as the level of the angle of the scapulae on both sides. The liver edge was palpable 3 cm. below the costal margin in the midclavicular line. There was swelling of the lower extremities.

The signs of congestive heart failure were attributed in part to the untreated irregularity which was confirmed by electrocardiograms to be that of auricular fibrillation.

Course and Progress.—On her first day in the hospital, the patient was given 9 c.c. of the tincture of digitalis in one dose. Because of her unusual history of attacks of palpitation which responded to medication at home, she was watched very carefully. Three days after the administration of a single dose of digitalis, her

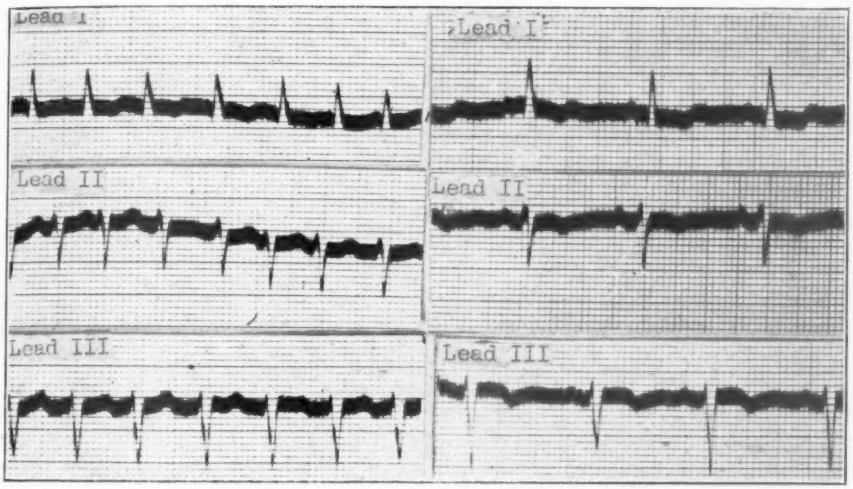

Fig. 2.—Case 2. Comparison records before and after the administration of a single dose of 12 c.c. of digitalis. Note the almost regular rapid ventricular rate during the presence of auricular fibrillation. The rate and rhythm returned to normal, three days after the drug was given.

heart rate and rhythm returned to normal, her dyspnea and cyanosis had disappeared, the swelling of her extremities had subsided, and the patient begged to be allowed out of bed. Between the time she had received her first dose of digitalis on Aug. 9, 1928, and the second week of September, 1928, the patient was kept off all medication except a mild laxative which she was allowed in daily doses.

Examination on Sept. 15, 1928, revealed that she was slightly dyspneic even at rest and that her heart rhythm was irregular, averaging 118 beats per minute. It was interrupted by many premature beats with compensatory pauses which were confirmed by the electrocardiograms to be auricular in origin. Four hours later, following the administration of 8 c.c. of digitalis almost all of the premature beats disappeared, the heart rate diminished to 90 beats per minute and on the following morning it was 65 and regular.

She remained well until Oct. 31, 1928, when I was notified that following some excitement and exertion she experienced a fainting spell for which she was put to bed. Examination at 11 A.M of that day showed her to be severely dyspneic and

cyanotic with her neck vessels pulsating tumultuously. The heart rhythm was almost regular but varied in rate between 210 beats per minute and 240 beats. Clinically it was very difficult to be sure that auricular fibrillation was present, but electrocardiograms taken then confirmed the presence of the arrhythmia.

Four days after the onset of this irregularity, the patient was given 12 c.c. of digitalis orally, which she was able to take only with difficulty. On the following morning, her apical rate was still irregular, but it now averaged only 100 beats per minute. Two days later (Nov. 5, 1928), electrocardiograms revealed the presence of sinus rhythm. After the establishment of the regular rhythm the patient was given a daily dose of 3 c.c. of the tincture of digitalis, and within 10 days she was clear of all her signs and symptoms of congestive heart failure that had developed very rapidly during the presence of the arrhythmia. The pulmonary edema had disappeared, the liver edge had receded to its original level of 2 cm. below the costal margin, the ascites and the swelling of the legs had all passed away.

In the ensuing few weeks, the patient was watched even more carefully than previously in order to see whether it would be possible to determine the causative factors and the mode of onset of her irregularities.

Exactly 16 days after she received her last dose of digitalis, she began to complain of shortness of breath which was more marked than previously. Her heart rate was irregular and averaged 110 beats per minute. A diagnosis of premature beats with compensatory pauses was confirmed by the electrocardiograms to be of auricular origin. A dose of 8 c.c. of digitalis abolished the arrhythmia and caused a slowing of the sinus rate to 56 beats per minute within 5 hours after its administration.

Between Dec. 4, 1928, and June 12, 1929, the date of her discharge from the hospital, the patient received daily doses of digitalis varying from 1 to 3 c.c. and never experienced any further attacks of irregularity of the heart. Throughout all this time, her ventricular rate was always about 60 beats per minute.

CASE 3.—S. R., a female, aged 61 years, was admitted to the Montefiore Hospital on Dec. 21, 1928. Her chief complaints were recurrent periods of shortness of breath associated with palpitation of the heart and weakness.

Previous Illness.—In the summer of 1928, the patient began to notice shortness of breath on moderate exertion and swelling of the lower extremities which has persisted since. In August, 1928, she became conscious of recurrent attacks of palpitation of the heart some of which would last as long as 5 hours and were frequently relieved by the continuous use of "green drops" prescribed for her by her physician. On Oct. 23, 1928, she entered the Presbyterian Hospital because of rapidly progressive swelling of the abdomen and lower extremities, shortness of breath and yellow discoloration of the skin.

Physical examination at that institution revealed a poorly nourished, deeply jaundiced old woman lying quietly in bed without dyspnea or cyanosis and looking chronically ill. The heart was enlarged both to the right and to the left sides, the apical impulse being in the sixth intercostal space in the anterior axillary line. Over this region there was a soft systolic murmur. A2 was accentuated. The heart rate was totally irregular.*

The lungs showed many moist râles at both bases posteriorly. The abdomen was large and there was shifting dullness. The liver and spleen were not palpable. There was moderate swelling of the lower extremities.

Shortly after her admission to the Presbyterian Hospital, a paracentesis of the abdomen was performed at which 3000 c.c. of opaque, yellow colored fluid were removed at one time.

*No note was made at the Presbyterian Hospital as to whether there was a pulse deficit present. However, it is definitely reported in this patient's chart that the irregularity was believed to have been due to premature auricular beats.

Between Oct. 23, 1928, and Dec. 6, 1928, she required three separate paracenteses of the abdomen for the relief of ascites. On her admission to the Montefiore Hospital, the patient still showed signs of dropsical effusion in both the pleural and abdominal cavities, and the heart rhythm was totally irregular, the ventricular rate averaging 120 beats per minute with a pulse deficit of 16 beats. Following rapid "digitalization" (16 c.c. in two days) the patient improved considerably so that within a few days after her admission, she was fairly comfortable. Particular note was made at this time (Dec. 24, 1928) that her heart rhythm had become regular and averaged 80 beats per minute.

Reëxamination on Jan. 18, 1929, approximately three weeks after the return of the sinus rhythm, revealed no evidence of any dyspnea, cyanosis, edema, or jaundice. The apical impulse of the heart was in the sixth intercostal space to the left of the midclavicular line. There was a short systolic murmur at the apex. A2 was accentuated. The heart rate was regular. The blood pressure was 190 mm. of mercury systolic and 90 mm. diastolic. The abdomen was soft and there was no evidence of shifting dullness. The liver edge was 4 cm. below the costal margin at the midclavicular line. The spleen was palpable 2 cm. below the costal margin. The legs showed slight pretibial edema.

Within one week the patient became ambulatory. She was able to be up and about until the morning of Feb. 8, 1929, when she had a severe attack. The electrocardiograms taken on this day showed auricular fibrillation with a very rapid ventricular rate. She received 9 c.c. of digitalis in one dose, and within two days there was a return to normal sinus rhythm and a disappearance of all symptoms of shortness of breath and signs of congestive heart failure.

For the next month she was placed under controlled observations, and repeated electrocardiograms were taken to determine, if possible, whether there was any relationship between the return of her symptoms and the onset of her irregularities and the disappearance of the digitalis from her system as judged by a return to normal of the S-T interval and the size, shape and form of the T-waves.

Changes in her rhythm, such as marked shifting of the pace-maker and the appearance of auricular premature beats, were observed to come on 17 days after she received the last dose of 9 c.c. of digitalis. At this time there was still evidence of negativity of the T-waves in Leads I and II, indicating probably that not all of the digitalis had been eliminated. During the presence of sinus rhythm it was possible definitely to maintain a relatively slow sinus rate by daily doses of 2 c.c. of digitalis.

From February, 1929, until May, 1929, the patient was ambulatory and did not require any further mechanical removal of fluids.

On the morning of May 14, 1929, the patient began to complain of breathlessness. She had not received any digitalis in the week prior to that time. Multiple auricular premature beats were found to interrupt and increase her ventricular rate. She was advised to stay in bed, and for the next two days there was a noticeable increase in the irregularity of her heart as well as in the breathlessness and the signs of congestive heart failure. On May 16, 1929, two days after the onset of the arrythmia, she showed auricular fibrillation with a ventricular rate averaging over 200 beats per minute. At 10 P.M. on the evening of this day, the patient became extremely restless, there were marked mental changes, pulmonary edema had set in, and at 10:40 P.M. she expired despite all attempts made to control her ventricular rate at that time.

DISCUSSION

The Type of Patients.—All of the patients studied in this series had evidences of organic heart disease for some time prior to the onset of the symptoms and signs associated with premature auricular beats and seizures of paroxysmal auricular fibrillation. The underlying

pathological lesions varied, three showed evidences of chronic rheumatic valvular heart disease, three had hypertension with mild signs of congestive heart failure and one had signs characteristic of multiple myocardial infarction.

Although as has been recently shown by Boas and Weiss[1] with the Cardiotachometer, the sinus rate in normal individuals is usually labile and influenced to a great extent by the extrinsic nerves of the heart, the sinus rates of these patients were particularly susceptible to these influences. They all showed marked diurnal and daily variations of their heart rates even while in bed. Rest in itself or rest in addition to sedative medications such as adequate doses of bromides and chloral and in some instances, morphine sulphate, could not effect the lability of the sinus rate or prevent the appearance of premature auricular beats.

It is very likely that the diseased heart muscle of these patients was a predisposing factor in the initiation of spontaneous premature auricular beats and the increase in sinus rates. For, while excitement, exertion and nervous disturbances were found to induce easily these extra auricular beats reflexly, it is well known that experimentally, direct or indirect stimulation of the cardiac nerves in themselves cannot initiate premature beats. Where premature beats have been demonstrated to follow stimulation of the sympathetic nerves or section of the vagi, they have invariably followed the use of substances known to increase the irritability of the heart.[2, 3]

The Effects of Digitalis on the Sinus Rate.—The administration of digitalis to these patients during the presence of sinus rhythm slowed the heart from an average rate of 95 beats per minute to 62. The presence and maintenance of a relatively slow sinus rate with normal rhythm were an essential requisite for their welfare; for, as can be gained from the protocols reported above, signs of congestive heart failure were greatest when the heart rate was irregular and rapid even in the presence of premature auricular beats. It was possible to maintain a relatively slow rate and regular rhythm and to prevent the marked lability of the heart rate normally noted, as well as the onset of the premature auricular beats, by the continued use of the drug in doses of 1 to 2 c.c. of the tincture per day.

In this respect these patients form a unique group, for by maintaining a sinus rhythm with a relatively slow rate by the constant use of digitalis from day to day, it was possible in every instance to prevent the onset of irregular heart action. Comfort was evident only in the presence of sinus rhythm, and no other drug could produce this effect except digitalis.

Contrary to general belief, the slowing of the ventricular rate during already established fibrillation was not accompanied by as much benefit even when the rate was as low as 60 beats, for signs of con-

gestive heart failure became increasingly marked even in the presence of the low rate as long as the action of the heart was irregular. Therefore the use of digitalis during the presence of sinus rhythm may be said to have acted here as a prophylactic drug and prolonged life by preventing the appearance of premature auricular beats and the paroxysms of auricular fibrillation with the severe accompanying signs of congestive heart failure ending at times in rapid death.

No quantitative relationship was observed between the administration of the drug and the changes in the electrocardiograms associated with digitalis administration. A diminution of the T-waves in all three leads with a lowering of the S-T interval below the iso-electric line appeared equally as well after 3 c.c. as after 10 c.c. of digitalis. The persistence of these signs in the electrocardiograms could not be taken as an index of digitalis action, since the disturbances in the sinus rate and rhythm were observed to appear even in the presence of maximum changes in the electrocardiograms usually associated with digitalis and after the drug had been withheld for several weeks. For example, in almost all of the patients the T-waves had not as yet resumed their normal shape when premature auricular beats began to disrupt the sinus rhythm.

The Effects of Digitalis on the Premature Auricular Beats.—Auricular premature beats whether coming singly, in coupled rhythm, or in groups of more at one time, could be easily eliminated in these patients by the effective use of digitalis. Conclusive proof that the administration of the drug was responsible for the abolition of the extra beats is the fact that invariably after their appearance the withholding of the digitalis would result within one to three days in the development of auricular fibrillation with a very rapid ventricular rate. The premature beats would not disappear any faster following the intravenous use of digitalis. Experimental attempts to induce premature auricular beats in these patients and to test out their abolition with digitalis intravenously were unsuccessful. Atropine did not induce premature auricular beats in four patients in whom it was tried in doses of gr. $\frac{1}{20}$ intramuscularly. In one case, however, not only was there an increase in the basic ventricular rate following its use, but showers of premature auricular beats were initiated by the drug within fifteen minutes after its injection, and these were followed by a very rapid irregular ventricular rate with auriculo-ventricular dissociation which lasted for several minutes but disappeared, however, very soon. Such action of atropine has already been observed in man, and the explanation for this phenomenon is based on unequal distribution of the action of the drug on the vagus endings, the fibers supplying the A-V bundle being paralyzed first, thus permitting the escape of the ventricular rhythm and resulting in dissociation of the auricles and ventricles.[4, 5]

Transitory irregular extrasystolic tachycardia of auricular origin was induced in two of the patients by the use of adrenalin even after digitalis had been used effectively to slow the sinus rate for several weeks. The effects of adrenalin were more marked in the patient in whom it was possible to induce the irregularity of the heart by atropine.

There were increasing symptoms of breathlessness and signs of congestive heart failure following the onset of the premature auricular beats.

In two of the patients in whom bigeminal rhythm had been established after the appearance of auricular extrasystoles, the administration of 6 c.c. of the tincture of digitalis to each one resulted in the abolition of the extrasystoles within four and four and one-half hours respectively.

Their disappearance under the influence of digitalis still remains a fertile field for speculation.

The Effects of Digitalis on Transient Auricular Fibrillation.—In every instance studied it was possible to show a direct relationship between the administration of a single large dose of digitalis and the disappearance of auricular fibrillation, with restoration to normal sinus rhythm following the use of the drug. For the persistence of the unusually high ventricular rate present in all, with which the auricular fibrillation was ushered in, was always accompanied by progressive signs of congestive heart failure, such as extreme breathlessness and hydrothorax, rapid edema of the legs, enlargement of the liver, ascites, and finally pulmonary edema. These events would take place in some patients more rapidly than in others, in the order mentioned beginning shortly after the onset of the arrhythmia and at times reaching alarming proportions within from twenty-four to forty-eight hours. When the pulmonary edema was overwhelming, no medication was of any benefit, and death would take place from asphyxia as was observed at the hospital in two patients. In three patients the irregularity was accompanied by profuse perspiration and symptoms of angina pectoris with radiating pains to the left arm and finger tips which persisted until the ventricular rate receded with the use of the drug.

The disappearance of the irregularity following the use of digitalis and the return to normal of the sinus rate and rhythm were accompanied by a spectacular recovery from the signs of congestive heart failure, all of which would disappear within two or three days after the return of the rhythm to normal.

The ventricular rate was always over 150 beats per minute when the auricular fibrillation set in, and the rhythm during this rapid rate was almost regular at times, exhibiting this regularity even in the electrocardiograms so that to one not accustomed to seeing these cases, a diagnosis of the tachycardia was difficult.

In one case that was followed constantly, both during the day and night, the administration of a single large dose of digitalis halved the ventricular rate of 210 within four hours after the medication was given orally, and within two hours when it was given intravenously at another time. This low rate of about 100 beats lasted for two days and then gradually came down to about the relative normal of 60 to 70 beats per minute when the transition to sinus rhythm took place as revealed by the electrocardiograms.

In several cases in which the digitalis was given orally in doses of 3 c.c. per day after the establishment of the auricular fibrillation the ventricular rate would also slow down but not until from 15 to 21 c.c. of the tincture had been administered. If further use of the drug was made, partial heart-block with a rate of 45 beats and premature beats of the ventricle with bigeminal rhythm due to them would set in, indicating the toxic action of digitalis. By withholding digitalis at such times there would be a gradual return of the rate to a level of from 60 to 70 beats per minute and then sinus rhythm would be established shortly afterward. The signs of congestive heart failure did not disappear as readily when small doses of digitalis were used to slow the ventricular rate.

Following the use of a single large dose of digitalis and the restoration of sinus rhythm, the onset of auricular fibrillation could always be prevented by maintaining a relatively low sinus rate with the constant use of daily doses of digitalis of from 1 to 3 c.c.

The transient nature of auricular fibrillation in patients with heart disease is now too well appreciated to require detailed comment. Its evanescent appearance and disappearance with only slight discomfort have been observed in certain patients over a period of years without adding to the seriousness of their prognosis. In many instances the subjects of these seizures were not even aware of anything being wrong with their cardiac mechanism. Consequently the benefits of the administration of any drug during these seizures in the absence of symptoms and signs is questionable.

In such patients, quinidine has, nevertheless, been found of unusual value not only in curing the arrhythmias but also in preventing them. Quinidine is, however, contraindicated in congestive heart failure judging from the unusually large series of deaths following its use at the Montefiore Hospital. It is therefore gratifying to learn that the administration of digitalis in single large doses given at one time may abolish auricular fibrillation with a very rapid ventricular rate in patients with the particular type of irregularity reported in this study.

The action of digitalis on the auricles being as complex as it is, no attempt is made to explain the restoration of sinus rhythm following the administration of the drug in these cases.

SUMMARY

Seven patients with organic heart disease are reported who were subject to recurrent attacks of auricular fibrillation with a very rapid and persistently high ventricular rate that did not slow with rest. In each instance this arrhythmia was preceded for several days by premature auricular beats, first coming on singly, then in groups of two or more at a time.

In most instances the premature auricular beats were easily induced by psychic, nervous or emotional disturbances. If they were allowed to continue, auricular fibrillation invariably developed after two or three days. The premature auricular beats could be abolished and the onset of the auricular fibrillation could be prevented by the administration of adequate doses of digitalis, either orally or intravenously.

The onset of these irregularities was always associated with progressive signs of congestive heart failure, such as extreme breathlessness, rapid enlargement of the liver, effusion in the serous cavities and pulmonary edema.

A large single dose of digitalis administered during the presence of an attack of auricular fibrillation resulted in the slowing of the heart rate within four to five hours when the drug was given orally, or within two hours when it was given intravenously. Restoration to sinus rhythm would not take place, however, until from two to three days after the administration of digitalis. All the signs and symptoms of congestive heart failure precipitated by the disturbances in rhythm would gradually pass away in the presence of sinus rhythm.

The administration of small daily doses of digitalis during the presence of auricular fibrillation, in several patients in whom this form of therapy was attempted, slowed the heart rate but did not abolish the arrhythmia or relieve the symptoms and signs.

Six of these patients were ambulatory and could carry on their daily restricted activities so long as sinus rhythm was present. A relatively normal sinus rate could be maintained in all by the use of digitalis in small daily doses during the presence of sinus rhythm. If the drug was discontinued for any length of time even when sinus rhythm was present, the premature auricular beats would reappear and be followed by auricular fibrillation with a very rapid ventricular rate. If the ventricular rate could not be controlled with digitalis, death would take place within a short time from asphyxia due to pulmonary edema.

Because of the unusual response of these patients to variable doses of digitalis in the presence of sinus rhythm as well as of auricular premature beats and auricular fibrillation, they form a distinct group among patients with heart disease and should be given special consideration when encountered in practise.

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THE SIGNIFICANCE OF SPLINTERING OF THE TERMINAL PORTION OF THE QRS DEFLECTION OF THE ELECTROCARDIOGRAM*

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CONSIDERABLE diagnostic importance has been attached to splintering or notching of various portions of the QRS complex. Such notching is usually associated with other electrocardiographic changes which render the records distinctly abnormal. A large bizarre QRS complex, notched, with a duration in excess of 0.1 second and T in the opposite direction completes the picture of a bundle-branch lesion. A notched QRS complex in all leads, low in voltage, is evidence of intraventricular block. In this study, however, we wish to limit ourselves to a discussion of splintering of the final deflection of the QRS complex as an isolated electrocardiographic phenomenon, and to point out the significance of such splintering.

A. M. Wedd[1] has already called attention to the significance of notching of the R-wave and states that this is frequently encountered in cases of unquestioned myocarditis. In Wedd's series of thirty cases, seventeen showed notching of R in Lead III alone; three showed the notching in all leads; four in Leads I and III; three in Leads II and III; two in Leads I and II; and one in Lead I alone. Although we agree that notching of the R in one or two leads may be of clinical significance we must admit that similar notching does occur in records of normal individuals.

The appearance of such notching in normal individuals has been pointed out by Lewis and Gilder.[2] In a study of fifty normal individuals they found notching of R_1 in three instances; of R_2 in one instance; of R_3 in six instances in which its identification was not complicated. They likewise found splintering of the S-wave in two instances in Lead II, and noted that apart from eleven cases of splintering in the opening events of ventricular systole, a division of S was never seen in Lead III. Wiggers[3] states that humping, notching or splintering of the R-wave is normal when it occurs on a small wave in a single lead, and when it occurs near the base of the ascending or descending limbs of two different leads.

In an effort to check the frequency with which splintering of the terminal part of the QRS deflection occurred in our series of normal records we examined the electrocardiograms of 119 known normal

*From the Medical Clinic and Electrocardiographic Laboratory of Mt. Sinai Hospital of Cleveland.

individuals. Such notching occurred in one or two leads in twenty-one cases of this series. It appeared in Lead I in five instances; in Lead II in eight instances; in Lead III in two instances; in Leads I and III in two instances; in Leads I and II in one instance; in Leads II and III in three instances. It is evident, however, that in the total of 119 normal individuals studied, in no instance did notching of the final part of the QRS complex occur in all three leads.

On the other hand, in a series of 4000 electrocardiograms taken from the files of Mt. Sinai Hospital we found splintering of the final part of the QRS deflection in all leads as the only electrocardiographic abnormality in 34 instances. In all cases where splintering occurred in three leads there was unquestionable clinical evidence of cardiac abnormality. The types of clinical cardiac abnormalities represented in these cases are as follows:

Hypertension	14 cases	41 per cent
Rheumatic heart disease	13 cases	38 per cent
Coronary arteriosclerosis	5 cases	15 per cent
Hyperthyroidism	1 case	3 per cent
Developmental defect	1 case	3 per cent

In these records with notching in all leads left preponderance occurred in 22 instances (65 per cent); right preponderance in 2 instances (6 per cent); no preponderance in 10 instances (29 per cent).

The actual cause of this splintering is a matter of speculation at present. We know that the QRS group of deflections corresponds to the excitation of the ventricles and that the conus and base of the left ventricle become electrically active at the peak of the R or a little later.[4] The terminal phase of the QRS complex is completed with excitation of both ventricles, and it is not unreasonable to assume that the notching is associated with an abnormality in the Purkinje conduction. This may be due to myocardial enlargement or endocardial changes—either of which might cause changes in the record of the course of excitation.

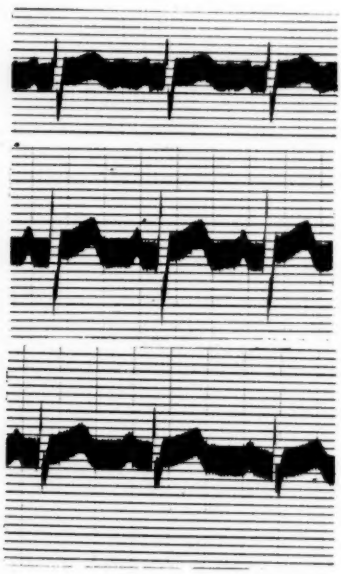
SUMMARY

A series of 119 electrocardiograms of 119 normal individuals has been studied and notching in the terminal portion of the QRS complex in all three leads has not been found in any of the cases. Thirty-four cases showing the presence of such notching in all leads have been studied, and it has been found that there is distinct evidence of cardiac abnormality in all instances. It is therefore concluded that an electrocardiogram which shows splintering in the terminal part of the QRS complex in all leads is distinctly abnormal. This finding has been present in various types of cardiac disease. Illustrative cases and records are shown.

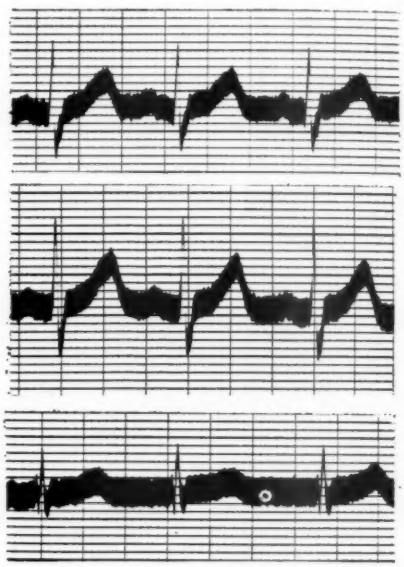
ILLUSTRATIVE CASES

CASE 1.—E. C. A white male of 8 years. Rheumatic fever at 5 years. Systolic and diastolic murmurs at apex. Orthodiagram shows straightening of middle left cardiac margin with elongation of the shadow of the left ventricle. Clinical Diagnosis: Rheumatic heart disease, mitral stenosis and insufficiency with normal exercise tolerance.

CASE 2.—D. K. A white female of 19 months. Not a blue baby. Pneumonia at age of 7 months. Musical systolic murmur, best heard along left sternal margin in second and third intercostal spaces. Also heard at apex. Orthodiagram shows definite mitral configuration with straightening of the middle left cardiac margin. Considerable bulkiness to right and left suggesting a congenital septal defect. Chest 16 cm. Transverse diameter of heart 8 cm. Clinical Diagnosis: Developmental defect.



Case 1.

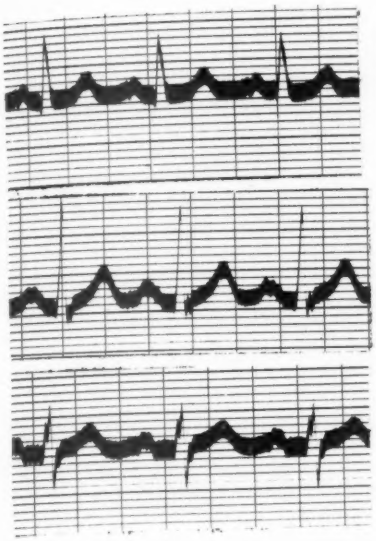


Case 2.

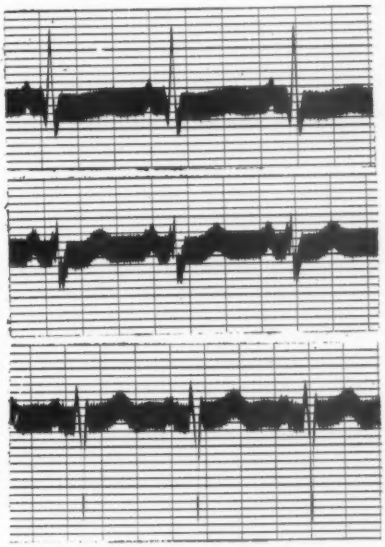
CASE 3.—F. D. White female of 16 years. Attacks of chorea at 7 years and 13 years. Loud systolic murmur at apex. Left border of cardiac dullness 10 cm. from midsternal line in fifth interspace. Orthodiagram shows mitral configuration with bulging of upper left cardiac margin and additional enlargement to right and left. Bulging of left auricle in right lateral position. Chest 23 cm. Aorta 3.5 cm. Transverse 13.5 cm. Clinical Diagnosis: Mitral insufficiency.

CASE 4.—N. G. White female of 62 years. Admitted to hospital in shock two days after severe pectoral pain. Diagnosis of coronary occlusion by one of writers. Notching appeared as first sign of abnormality in electrocardiogram. Later electrocardiographic signs of coronary occlusion appeared. Clinical Diagnosis: Coronary sclerosis with occlusion of coronary artery.

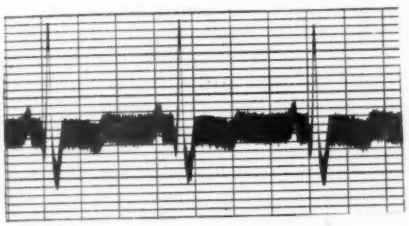
CASE 5.—M. G. White female of 69 years complaining of precordial pain. Increased palpable precordial activity. Right border of cardiac dullness 1 cm. to right of sternum. Left border of cardiac dullness 2 cm. to left of midclavicular line in fifth interspace. Harsh systolic murmur over entire precordium. Blood

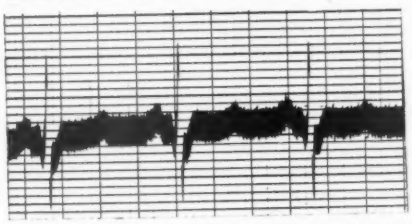


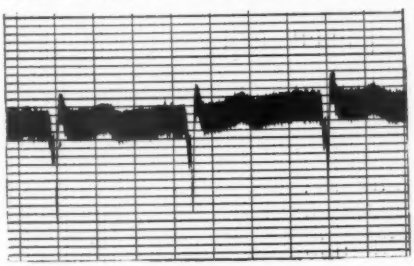
Case 3.



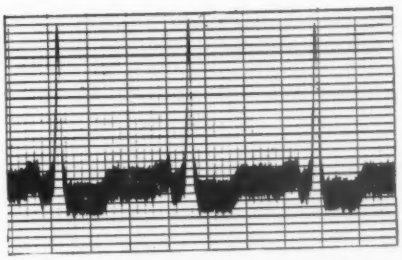
Case 4.

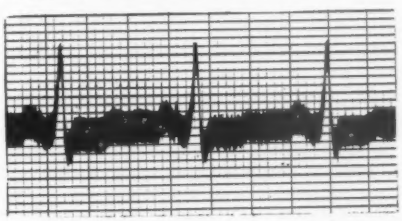


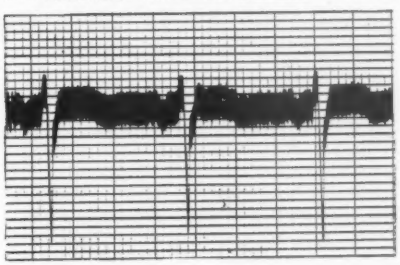




Case 5.





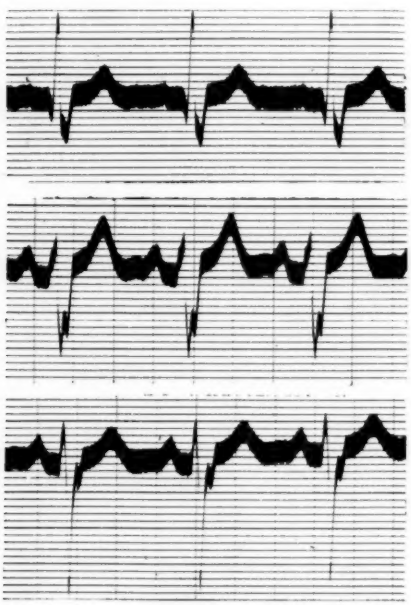


Case 6.

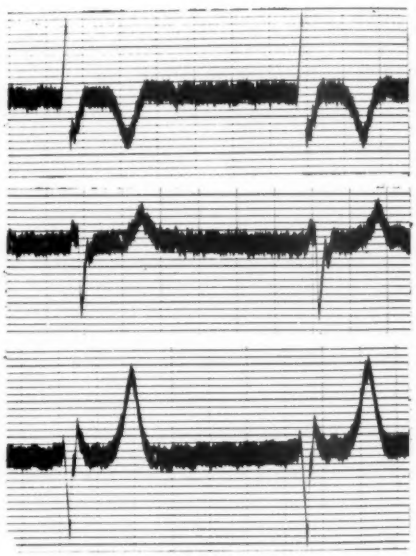
pressure 210/120; 178/86; 190/110; 160/76. Clinical Diagnosis: Hypertension with cardiac hypertrophy.

The following autopsied cases are presented. These show the splintering of the terminal portion of the QRS deflection in the presence of other electrocardiographic abnormalities.

CASE 6.—L. W. A white female of 60 years admitted to the hospital complaining of shortness of breath and high blood pressure of two years' duration. Has taken antiluetic treatment for the past seven years and malaria treatment for general paresis three years ago. Presented picture of congestive heart failure with enlargement of the left ventricle. A faint diastolic murmur was heard at the aortic area. Blood pressure 240/90; 200/90; 190/90. Changed from normal mechanism to auricular fibrillation during hospital stay and went downhill rapidly. No digitalis had been administered at time of first electrocardiogram. Orthodiagram shows tremendous enlargement to the left with considerable diffuse dilatation and marked increased density of the aorta. Chest 26 cm. Transverse 16 cm. Aorta 9 cm. Clinical Diagnosis: Hypertension with cardiac hypertrophy, luetic aortitis with insufficiency.



Case 7.



Case 8.

Anatomical Diagnosis: Hypertrophy and dilatation of the heart (chiefly left ventricle); (Heart weight 800 grams); luetic mesaortitis with involvement of the leaflets and slight insufficiency; generalized arterial and arteriolar sclerosis.

CASE 7.—M. N. A white male of 56 years admitted complaining of fainting spells of six months' duration. Patient presented the large head and bowing of the long bones typical of Paget's disease. Modern enlargement of the left ventricle with a musical systolic murmur at the apex. Blood pressure 176/80. During fainting spells heart mechanism would change from normal to block. Developed congestive failure and expired. Orthodiagram showed enlargement of heart to left.

Clinical Diagnosis: Generalized arteriosclerosis; heart-block; congestive heart failure; Paget's disease. Anatomical Diagnosis: Calcium deposits mitral and aortic

valves involving conduction system; mitral stenosis, considerable; aortic stenosis, moderate; hypertrophy of myocardium, weight 460 grams.

CASE 8.—N. A. White male of 71 years admitted because of fractured skull. Heart enlarged, arrhythmic, no murmurs. Became stuporous, cyanotic and expired. Clinical Diagnosis: Fractured skull, auricular fibrillation. Anatomical Diagnosis: Fractured skull; cardiac hypertrophy and dilatation, weight 550 grams; moderate atherosclerosis of coronary arteries with several areas of scarring in myocardium.

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SINO-AURICULAR BLOCK*

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SINO-AURICULAR block is a rather rare form of cardiac arrhythmia. The condition was first described by Wenckebach[1] in 1907, and a comprehensive review is given by Levine[2] of fourteen cases published before 1916. Levine, in his review, adds four cases of his own. Barlow[3] reviews thirty-two cases which had appeared in the literature from 1916 to 1926 and also adds four cases. White and Viko[4] reported only eleven cases in 3219 electrocardiograms taken at the Massachusetts General Hospital from 1914 to 1922. The condition, however, is probably more common than is suspected (Levine,[2] Smith,[5] White[6]).

The most common form of the abnormality is that of an occasional dropped beat. It is unusual to find two or more beats dropped out in succession. Levine[2] reports one such case where five beats were dropped out, and in the series reported by Barlow no mention was made of any such case. Although delayed A-V conduction is quite frequently associated with S-A block, and is emphasized by Lewis[7] who says that it is too frequent to be accidental, it is rare to have conduction so impaired that a ventricular beat is dropped.

A case of S-A block with one and two dropped beats and delayed A-V conduction with a dropped ventricular beat is here reported.

CASE REPORT

Miss L. S., aged 30 years, a stenographer, entered the hospital September 9, 1929, complaining of shortness of breath, palpitation, and edema of the lower extremities. About three years before, the patient had had an attack of influenza, and about two months following this she noticed that on slight exertion she would become short of breath. This was her first intimation of any heart trouble. Since then her activities had been greatly restricted because any overexertion caused shortness of breath and decompensation. The patient had had chorea twice, at the ages of 5 and 9 years, and had had many sore throats before her tonsils were removed in 1922.

Physical examination on admission showed a slightly undernourished female. The heart was slightly enlarged to the left and right, and there were a systolic thrill and diastolic shock palpable over the precordium. A late diastolic and systolic murmur were heard along the left sternal border, with an accentuated pulmonic second. The rhythm was regular, and the blood pressure was 100/68 mm. There were scattered râles at both bases, and there was slight pitting edema over both lower extremities. The white blood count was 10,200; the erythrocytes, 4,210,000; hemoglobin, 75 per cent (Sahli), and the urine was negative. Digitalis folia, gr. 3 daily, was given the patient and, with rest in bed, cardiac decompensation disappeared, and the patient was discharged much improved September 10, 1929.

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The patient was readmitted to the hospital October 12, 1929, because of cough and sore throat. After four days' rest in bed and local treatment for an acute nasopharyngitis she was greatly improved and left the hospital against advice. She returned three days later (October 19) with bronchitis and remained in the hospital until October 24, 1929. During this stay, she showed no signs of decompensation.

On January 27, 1930, the patient was readmitted to the hospital. One week before, she had had an attack of "influenza" followed in three days by painful joints. Examination at this time showed a liver which was just palpable and somewhat tender. The heart was the same as on previous examinations. There were tenderness and swelling of the right elbow and left ankle. The patient was put on salicylates and digitalis folia, gr. 1 b.i.d. The arthritis did not spread and the

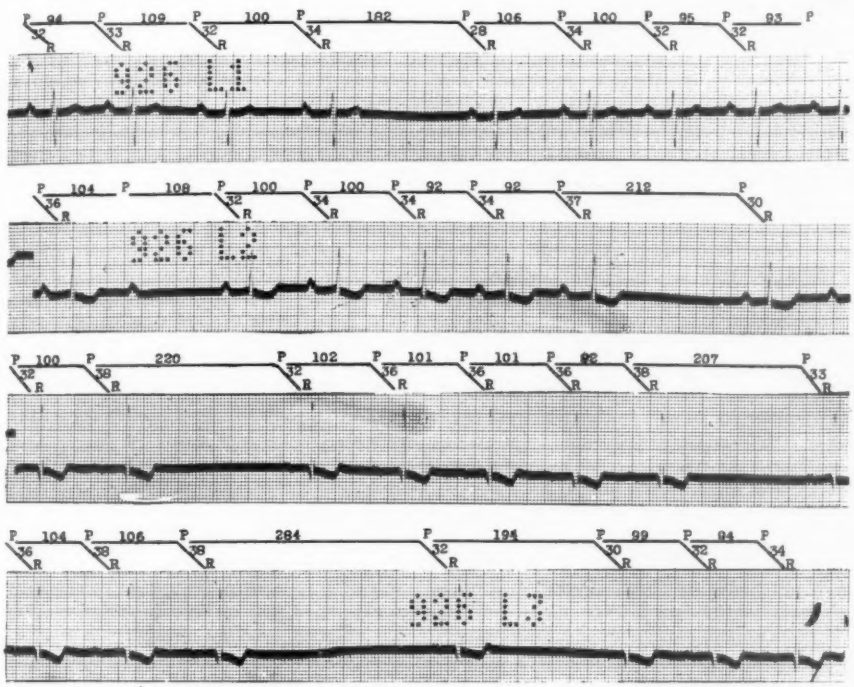

Fig. 1.—Electrocardiogram taken on February 19, 1930. Top strip, Lead I; next strip, Lead II; two lower strips are from Lead III. Above each strip is plotted the P-P and P-R intervals.

patient improved. On February 7, 1930, an irregularity of the pulse was noticed for the first time. The patient was conscious of this irregularity and said that her heart was "skipping beats." An electrocardiogram was taken which showed sino-auricular block. The patient insisted on leaving the hospital the next day against advice and was told to stop the digitalis which she had been taking more or less constantly since her first admission to the hospital.

On February 18, 1930, the patient was admitted at 9:30 P.M. Since her discharge ten days before she had been taking digitalis "occasionally." The day before admission she had developed frequency and pain on urination. Examination at this time showed the liver very tender and down to the umbilicus. The left elbow was painful and swollen. There was marked edema of both lower extremities. The heart showed a cardiac irregularity similar to the one of February 7, the regular

rhythm being interrupted by a dropping of one or two beats. The urine showed one plus albumin and many white cells. An electrocardiogram taken the next morning (Fig. 1) showed sino-auricular block. Atropine sulphate, gr. 1/75, was injected subcutaneously, and twenty minutes later another electrocardiogram was taken (Fig. 2) which showed complete disappearance of the S-A block with a quickening of the rate. The urine gradually cleared, the edema disappeared, and the patient was once more made comfortable. The heart was regular and no evidence of S-A block was ever noted after the atropine had abolished it. The patient was discharged on March 8, 1930, and has not been heard from since.

DISCUSSION OF ELECTROCARDIOGRAMS

In Figs. 1 and 2, the electrocardiograms taken on February 19 are shown. The record obtained on February 7 resembles Fig. 1 in prac-

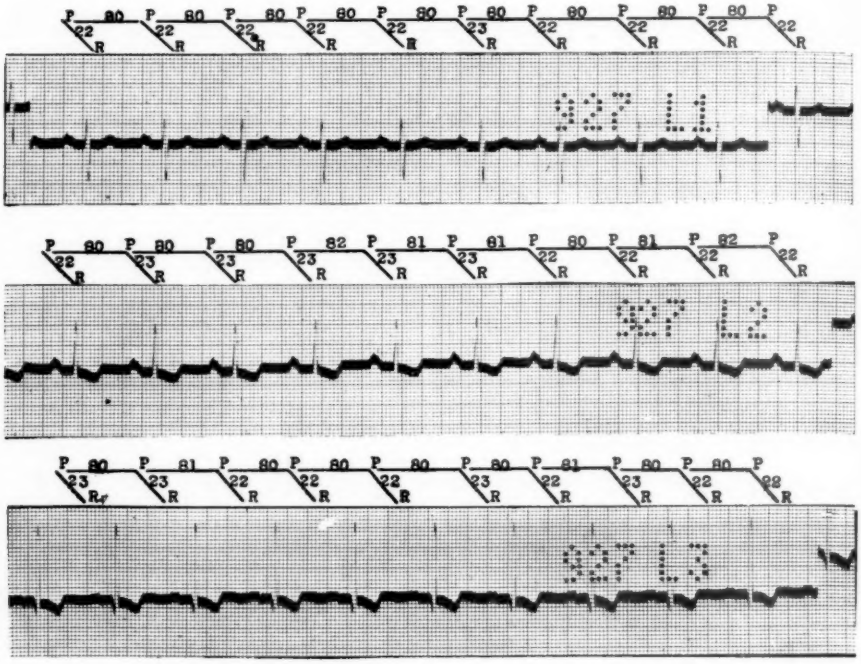

Fig. 2.—Electrocardiogram taken on February 19, 1930, twenty minutes after the administration of the one-seventy-fifth of a grain of atropine sulphate.

tically all respects except that no dropped ventricular beat was found. Above each curve in Figs. 1 and 2, are plotted the P-P and P-R intervals in hundredths of a second for ready reference. There is present in Fig. 1 a right ventricular preponderance as indicated by the inversion of the QRS in Lead I. There is some slurring of the R in Lead II. The P-wave is notched in all three leads, and a typical digitalis inversion of the T-wave is seen in Leads II and III. The P-R interval is prolonged, ranging from 0.32 to 0.38 of a second, and in Lead II there is a dropped ventricular beat. A sinus arrhythmia is present, and occasionally a long pause occurs which is equal to two

or three times the average cycle. Thus in Lead I the fourth P-P interval is equivalent to twice 0.91 of a second; in Lead II the fifth P-P interval is equivalent to twice 1.06 of a second; the long pauses in the two strips of Lead III are equivalent to twice 1.10 of a second, twice 1.035 of a second, thrice 0.913 of a second and twice 0.97 of a second, respectively. These figures are well within the variation present in the shorter P-P intervals, which vary from 0.92 to 1.09 of a second. Therefore, there can be little doubt that the longer pauses are due to so-called sino-auricular block. The longer pauses in the electrocardiogram taken on February 7 were also multiples of the shorter cycles, i.e., the longer P-P intervals were twice 0.89 of a second, twice 0.825 of a second, thrice 0.907 of a second, twice 0.89 of a second, twice 0.885 of a second, twice 0.94 of a second, twice 0.885 of a second and twice 0.90 of a second respectively. These values are within the range of the shorter P-P intervals, namely from 0.80 to 1.00 of a second. These observations indicate the presence of sino-auricular block in this record also.

It is interesting to observe that following the long pauses, the P-R interval shortens for one or two cycles, just as it does when a ventricular complex is dropped out (Fig. 1). Unlike the cases reported by Levine,[2] when two pauses come together in this case, the second is shorter (Fig. 1, last strip).

An attempt was made to evaluate the rôle played by the vagi by giving the patient one seventy-fifth of a grain of atropine sulphate after Fig. 1 was taken. A record twenty minutes later (Fig. 2) showed a complete disappearance of the sino-auricular block, together with the sinus arrhythmia. At the same time the P-P and P-R intervals shortened somewhat. However, the configuration of the complexes of the electrocardiogram remained essentially unchanged. This effect of atropine would indicate that the sino-auricular block was caused by a vagal effect probably as a result of the action of digitalis. Since the sino-auricular block—so-called—was associated with a delayed conduction in the A-V node and since both were alleviated by atropine, it would appear that the change in the sinus node in this case is in the nature of a conduction disturbance rather than of absence of impulse initiation.

SUMMARY

A case is presented which shows sino-auricular block with single and double dropped beats, associated with a prolonged A-V conduction and an occasional dropped ventricular beat. The sino-auricular block was relieved and the A-V conduction improved by atropine indicating that the sino-auricular block was a vagal effect presumably due to digitalis.

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THE MYOCARDIUM IN YELLOW FEVER

I. The Myocardial Function in Experimental Yellow Fever*

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INTRODUCTION

AMONG the changes in myocardial function occurring during the course of yellow fever, bradycardia has been noted most frequently by clinical observers. Although Delmas[14] in his treatise on yellow fever published in 1822 described this phenomenon, it remained for Charles Faget[20] to study accurately and to chart its behavior. He promulgated the law of a slowing heartbeat with a rising temperature in the early days of yellow fever, so that this seeming paradox became known as Faget's sign. It was confirmed by his confrere Touatre[62] and by later observers.[56, 12, 57, 5, 30, 21, 44, 43] Retardation of the heart rate in yellow fever has also been recorded with considerable constancy by most recent workers in this field. It has been described by Noguchi[48] and by Elliott[19] as existing in cases of the disease met with in Guayaquil, Ecuador, in 1918. Selwyn-Clarke[58] and Aitken,[1, 2, 3] as well as Mahaffy, Walcott, and Klotz,[28] observed the sign during the course of the disease in British West Africa in the years 1925 and 1926. The existence of this finding in the yellow fever of Senegal has been reported by Lasnet,[29] a French contemporary of these observers.

Investigation of the type and causation of the bradycardia occurring in yellow fever has been the basis of the experiments of several workers. In 1921 Cohn and Noguchi[10] first attempted to record and differentiate the type of bradycardia in experimental animals with the aid of electrocardiography. Unfortunately their results upon monkeys and guinea pigs inoculated with *Leptospira icteroides* and *Leptospira icterohaemorrhagiae*, in the light of our present knowledge, must be related to the functional pathology of Weil's disease rather than to that of yellow fever. Cannell,[6] in 1928, pointed out that bradycardia occurred in this disease independently of jaundice. The same author noted fatty degeneration in the auriculo-ventricular bundle and suggested that the occurrence of auriculo-ventricular dissociation might offer a possible explanation of the slow pulse rate in the disease. During the epidemic of yellow fever in Rio de Janeiro in 1928, Chagas[8] described a clinical picture occurring in from 10 to 15 per cent of his

*These studies have been performed under the tenure of a grant from the Banting Research Foundation. Their accomplishment has been possible because of the facilities made available in the Yellow Fever Laboratory of the International Health Division of the Rockefeller Foundation, at the Rockefeller Institute for Medical Research, and in the Physiological Laboratory of the Hospital of the Rockefeller Institute. The author is greatly indebted to the courtesy shown him by the directors of these laboratories, Dr. W. A. Sawyer and Dr. A. E. Cohn. During the absence of Dr. Cohn, Dr. H. J. Stewart kindly provided necessary facilities for the work.

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patients, more frequently among those who recovered, which he termed a suprarenal syndrome of the disease. The symptoms which this observer ascribed to an adrenal origin were profound debility, peripheral vasodilatation with redness of the face, dermographism, frequent capillary hemorrhages, arterial hypotension, bradycardia, and less often dissociation of cardiac rhythm. The following year Chagas and de Freitas,[9] in electrocardiographic studies of human cases, reported the occurrence of bradycardia and rarely of auriculo-ventricular dissociation. This latter phenomenon was assumed to be due to the influence of the vagosympathetic system.

TECHNICAL METHODS

Graphic Methods of Investigation.—A series of twenty animals was employed, of which seventeen belonged to the species *Macacus rhesus* and three to the species *Macacus cynomolgus*. Electrocardiographic tracings were taken of the cardiac action in these animals before inoculation with yellow fever virus. After a period varying from one hour to forty-eight hours after the registration of the normal electrocardiograms for each monkey, the animal was inoculated intraperitoneally or subcutaneously with 0.5 c.c. of fresh infectious monkey blood (Asibi virus) withdrawn by cardiac puncture from an infected animal on the first day of fever. Upon frequent occasions, when virus in this form was not available, a quantity of desiccated blood, the preserved form of the Asibi virus,[55] equivalent to 0.5 c.c. of whole blood, was dissolved in Locke's solution and used for the inoculation. Electrocardiograms were obtained whenever possible upon these animals during the period of incubation, and upon successive days of the disease. Frequently during the latter days of the illness tracings were taken twice daily.

The monkeys were anesthetized in each instance five minutes before being electrocardiographed. In securing electrocardiograms upon the first four animals, sodium iso-amyl-ethyl barbiturate, administered in solution intraperitoneally, was used as an anesthetic. Since in these earlier experiments it was observed that, with the daily employment of this anesthetic, the experimental animals died at the end of a period of time twenty-four to forty-eight hours shorter than the average duration of illness in the monkey inoculated with Asibi virus, and before the development of well-marked yellow fever lesions in the viscera, it was abandoned to be replaced by ether. The dosage of the former drug used to produce anesthesia in an animal amounted to 0.05 gram per kilogram of body weight. All electrocardiograms were taken with the animals in a supine position with four points of the skeleton, the two scapular spines and the two ischial tuberosities, in the same horizontal plane.

The electrocardiograms were recorded from the three standard leads. In this place it may be noted that Lewis[35]: found no conspicuous differences between the levo- and dextrocardiograms in man and monkey. One animal, a *Macacus cynomolgus* which developed peritonitis during the course of the experiments, was subjected to electrocardiography on successive days of the disease preceding death. The electrocardiograms on this monkey, which did not receive yellow fever virus, are offered as controls. In all, 256 tracings were obtained upon this series. Of 19 animals inoculated with the virus, 17 died of yellow fever, while 2 recovered from the disease. Following the completion of each physiological experiment and the death of the animal, a post-mortem examination was made. The heart was removed, and its cavities were opened in such a manner as to preserve intact the sino-auricular node and the auriculo-ventricular bundle. The whole cardiac tissue was then fixed in Zenker's fluid. Sections were also taken of the liver, kidney, and spleen in each case for the purpose of verifying microscopically the existence of yellow fever lesions in these organs.

Surgical Methods of Investigation.—The hypothesis of vagus nerve stimulation as the cause of bradycardia, suggested by some writers,[9] obviously necessitated investigation. Two monkeys were obtained at death, and dissections were made of the cervical and thoracic portions of the vagus nerve in order to obtain a familiarity with its course and distribution in *Macacus rhesus.* Ten animals were then selected for the elucidation of the problem. Six of these monkeys had been infected with yellow fever virus and formed a group of a larger series in which the development of slow heart action had been noted. Electrocardiograms designed to record the existing bradycardia were taken on these animals before submitting them to the operation of bilateral vagus section. In one experiment electrocardiograms were recorded after the vagi had been isolated and were about to be cut. In all experiments vagus section was performed immediately after the preliminary recording of the electrical changes accompanying the heartbeat. Electrocardiograms were taken again directly after the vagus section operation, and frequently additional ones were obtained from ten to fifteen minutes later. The remaining four animals of the group of ten monkeys relegated to the study of the problem of vagus effects were monkeys in apparent health upon whom vagus section was performed for purposes of control. In this series as well, tracings were taken immediately antecedent and subsequent to vagus section. Both the surgical and electrocardiographic procedures were carried out under ether anesthesia. After the completion of each vagotomy experiment the animal was killed by the continued administration of ether.

The operation of vagus section was performed first on the right vagus nerve and then on the left. Section of the nerve was carried out at the point where the superior belly of the omohyoid muscle crossed the common carotid artery. In man, most of the rami cardiaci superiores arise from the vagus trunk below this level, while all the rami cardiaci inferiores arise either from the right vagus and recurrent laryngeal nerves or the left recurrent laryngeal nerve below this point.

However, this method of bilateral vagus section would not insure the cutting of those few fibers which may sometimes arise from the superior laryngeal nerve. I am unable to say whether such fibers exist in *Macacus rhesus.* The method of abrogating vagus function by section of the two main trunks was chosen in preference to the more usual one of atropinization, because it would seem to offer more certain and less controvertible results.

Following the completion of these physiological experiments, autopsies were performed upon the animals. The hearts were carefully excised from the bodies, so as to include the muscle at the junction of the superior vena cava with the right auricle. After removal of each heart, its cavities were opened, and the entire cardiac tissue was fixed in Zenker's fluid.

RESULTS

1. *Physiological observations upon the sino-atrial node and vagus nerve.*

The observations upon the cardiac rate demonstrated that bradycardia is a constant finding in experimental yellow fever in the monkey. It was absent in only one instance, that of *M. rhesus* 15, in which cardiac puncture and the attendant deprivation of blood had been instrumental in producing the early death of the animal. In *M. rhesus* 8, there existed normally a very slow heart rate. The rate increased markedly on the third day of the incubation period, after which it became retarded and continued so during the further course of the disease. The bradycardia was found to be for the most part a progressive one, the heart rate diminishing from day to day of the disease and even from morning to afternoon of the same day. Occasionally the

TABLE I

HEART RATE OF MONKEYS EXPERIMENTALLY INFECTED WITH YELLOW FEVER VIRUS

MONKEY NUMBER	NORMAL RATE	DAYS OF INCUBATION			FIRST DAY FEVER		SECOND DAY DISEASE		THIRD DAY DISEASE		FOURTH DAY DISEASE		FIFTH DAY DISEASE		RECOVERY PERIOD
		1	2	3	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	
1	189					177	205	136	D						
2	208								212		150	D			
3	188					216	160	118	D						
4	250				216		189		204	D					
5	202			167	177		182	D							
6	217				270		233		197	180	D				
7	200						215		186		153		180	D	
8	160			223	186		170								211
9		213					193		162	D					
10	210						218		197	147	D				
11	223								160		152				191
12	205								168		80	D			
13	191							173	D						
14	213								173	144	D				
15	221					230*	D								
16	232								174	D					
17	226								34†	D					
18	228	226					204		150	D					
19									162	D					
20	171					228	222	186	D						
Control															

*Bled from heart, animal died.
†Animal died during inscription of Lead III.
D—Animal dead.

rate was rapid during the early days of the fever, but it was never accelerated in the end stages. When recovery took place, the heart rate regained its normal frequency. Bradycardia was absent in the severe infection of the peritoneum which killed the previously mentioned *M. cynomolgus* after a period equal to the average length of illness of monkeys dying as a result of infection with the Asibi virus.

It was characteristic of the course of experimental yellow fever in this series of animals that the heartbeat remained regular in its occurrence. Only twice was disturbance of rhythm met with during the course of the disease. An irregular cardiac function was observed in the dying heart of *M. rhesus* 17, in which animal the heart stopped beating during registration from the third electrocardiographic lead. In *M. rhesus* 12, on the morning of the fourth and last day of the disease, when the heart rate had become slowed from the normal of 205 beats per minute to 80 beats per minute, the rhythm became a little

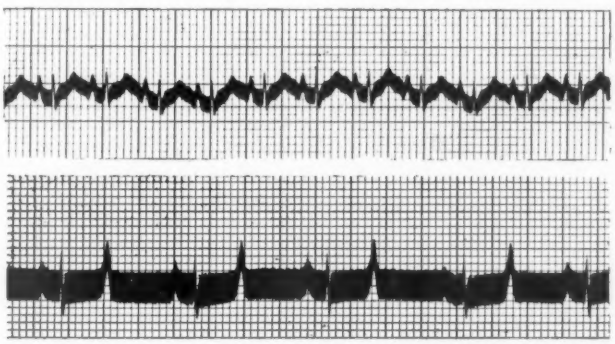


Fig. 1.—Bradycardia of yellow fever. Upper tracing shows the heart rate and the duration of the P-R period in *M. rhesus* 12 before inoculation with the virus. Lower tracing represents the degree of bradycardia and the lengthened P-R interval in the same animal on the morning of the fourth day of the disease (Lead II).

irregular. So slight was this change that it could not have been detected except by graphic methods of registration; the variations in the intersystolic periods were never greater than 0.08 of a second. The difference in length between intersystolic periods in the rhythm of this heart ranged from 0.04 to 0.08 of a second. Table I which presents the variations in cardiac rate from day to day of the disease, as measured by electrocardiography, and Fig. 2 which presents the same data in graphic form, give a better conception of these changes than could be obtained from further description. Recourse may also be taken to the serial cardiographic tracings (Figs. 7 and 8) which depict among other occurrences the lengthening of the intersystolic period in some of these animals during the later course of the disease. The slowed heart rate, as compared with the normal, is also well shown in Fig. 1.

The effect upon the existing bradycardia of cutting the vagi is of peculiar interest. The results of the experiments in which this opera-

tion was performed demonstrate that the bradycardia occurring in rhesus monkeys during the course of their illness from yellow fever persists after bilateral section of the vagus nerves. In only one animal was vagus section followed by a heart rate more rapid than that existing before the operation; in this case a bradycardia of 80 beats per minute was replaced by one in which 104 cycles were recorded

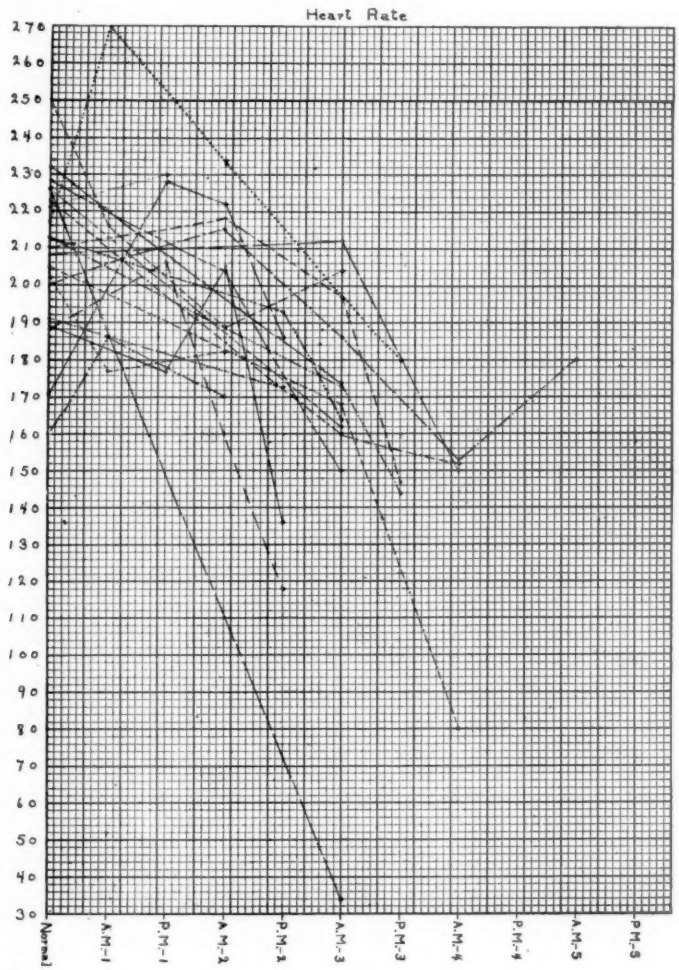


Fig. 2.—The heart rates of the various animals studied in the series of physiological experiments have been represented graphically from day to day of the disease. The abscissae represent the time of the disease measured at twelve-hour intervals; the ordinates represent the rates of heartbeat. The curve for each animal is drawn in a different type of solid or broken line. The progressive nature in the development of the bradycardia is well shown in the downward trend of most lines toward the later days of the disease.

during the same period. It should be borne in mind, however, that the later recorded rate of 104 was still half the original cardiac frequency and represented a most marked bradycardia. In one instance in this series the heart rate remained the same before and after vagus sec-

tion, while in the other four instances it was even less following the operation than previously. The explanation of this latter effect is problematical, but may possibly be related to a slower filling of the heart chambers associated with the very much slower respiratory rhythm. A slight lengthening of the conduction time, as represented by the P-R interval of the electrocardiogram, was noted in five of the ten experiments. This increase in the P-R period was never greater than 0.02 of a second. Its occurrence recalls the effect of vagal section or of atropinization in increasing the A-V block which follows rapid auricular action.[38] With regard to this consideration it may also be noted that in the dog's auricle in many circumstances in which the transmission intervals are long, vagal stimulation shortens these and, where actual block exists, partially or wholly relieves the condition.[37, 39, 36, 15, 16] In the remaining five experiments the conduction time was in one instance shortened, and in three instances unchanged, following the cutting of the vagi. The evidence of the control experi-

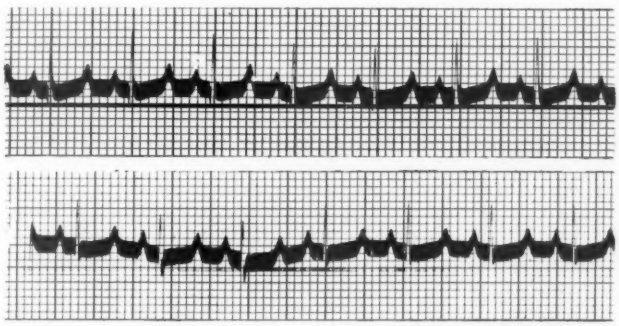


Fig. 3.—Independence of the bradycardia of yellow fever of vagus nerve influence. Upper tracing represents the heart rate in *M. rhesus* 2 before bilateral vagus section. Lower tracing shows the heart rate in the same animal following vagotomy.

ments suggests that even in normal monkeys the vagus nerve exerts little effect upon the heart rate during ether anesthesia. The latter suggestion is in keeping with the finding of Gold, Gryzwacz, and Nowicki[22] that ether by inhalation, in doses that do not paralyze respiration, depresses but does not completely paralyze the vagi. In these control animals the heart rate was in two instances unaltered, on one occasion slightly raised, and upon another slightly lowered, following bilateral vagus section. Vagus influence upon the heart rate is known to be very fluctuating.[46] It is very well marked in the dog and to a lesser degree in man.[17] Vagus tone varies from species to species,[59] from animal to animal within the same species, and from time to time within the same animal. As Wenckebach and Winterberg[63] have pointed out, the bradycardia of sino-atrial origin is different from that responsible to vagus influence in that the former is a regular one, while the latter is irregular in its rhythm. It may be noted that the slow heart rate of yellow fever persists during anesthesia induced by

sodium iso-amyl-ethyl barbiturate given intraperitoneally in a dosage of 0.05 gram per kilogram of body weight. This result was consistent in the four animals of this series on which the drug was used. The amount given to one animal frequently equalled 100 to 150 milligrams, depending upon its weight. Lieb and Mulinos[42] have shown that when 20 milligrams of sodium iso-amyl-ethyl barbiturate are

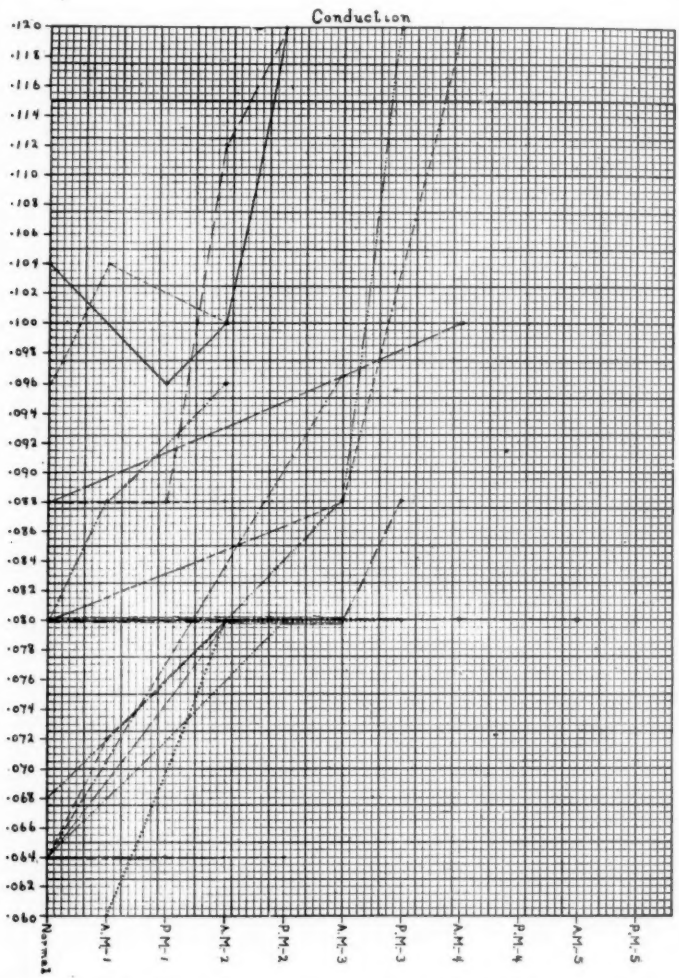


Fig. 4.—The conduction times, as measured by the P-R intervals of the electrocardiograms, of the various animals studied in the series of physiological experiments have been represented graphically from day to day of the disease. The abscissae indicate the time of the disease process measured at twelve-hour intervals; the ordinates represent the time values of the P-R intervals measured in decimals (thousandths) of a second. The curve for each animal is drawn in a different type of solid or broken line. A progressive but not a constant trend toward lengthening of the conduction time during the progress of the disease is well shown.

given intravenously to a cat, prolonged, but temporary, paralysis of the vagus fibers to the heart results. These considerations are cited because it is believed that the evidence points to the concept that the

TABLE II

EFFECT VAGUS SECTION ON BRADYCARDIA OF MONKEYS EXPERIMENTALLY INFECTED WITH YELLOW FEVER VIRUS

MONKEY NUMBER	BEFORE VAGUS SECTION		AFTER VAGUS SECTION	
	HEART RATE*	CONDUCTION† TIME	HEART RATE	CONDUCTION TIME
6	180	0.08	156	0.088
2	150	0.10	150	0.104
16	174	0.08	158	0.10
7	180	0.08	172	0.08
9	135	0.08 0.096‡	120	0.08
12	80	0.12	104	0.14
21 C	222	0.08	225	0.08
22 C	246	0.056	234	0.06
23 C	202	0.12	235	0.10
24 C	252	0.08	252	0.08

*Heart rate recorded in beats per minute.
†Conduction time as indicated by P-R interval of the electrocardiogram, recorded in decimals of a second.
‡Traction on vagi.
C—Control experiment.

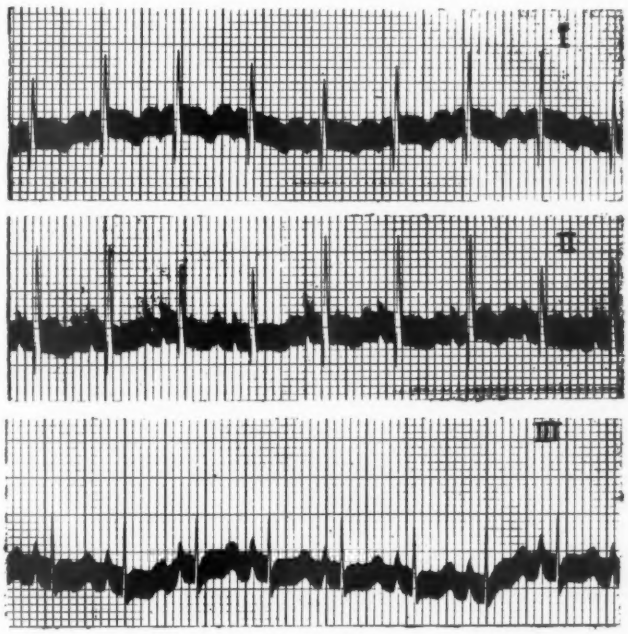


Fig. 5.—Electrocardiograms of yellow fever. Tracings from *M. rhesus* 12 on the morning of the third day of the disease. Note negative P_1 and T_1 deflections.

bradycardia of yellow fever is independent of vagus influence. Table II summarizes the results of the vagus section experiments; and in Fig. 3 electrocardiograms of the existing bradycardia in *M. rhesus* 2, before and after vagus section, are represented.

2. *Physiological observations upon the auricular muscle.*

Careful study of the character of the P-deflection during the course of the disease disclosed an infrequency of changes which could be

definitely recognized as abnormal. Nevertheless, in those infrequent instances when alterations in this wave were encountered, they were of the most profound kind. On two occasions in one animal (*M. rhesus* 4) the P-wave was reduplicated in Lead III during the first and second days of the disease. In another monkey (*M. rhesus* 6), it was found to be doubled in the tracing of Lead II, on the morning of the second day of the malady. In neither animal did these variations in the P-wave persist during the later progress of the infection. The reduplication of the P-deflection was in these instances inconstant from cycle to cycle, and frequently the second P-wave was observed to be negative in direction, thus imparting a diphasic character to the auricular tracing. Apart from these observations, purely negative P-waves occurred at one period of registration in the electrocardio-

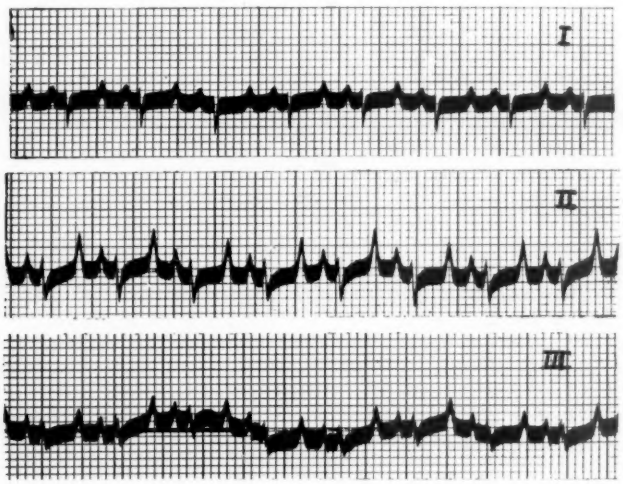


Fig. 6.—Electrocardiograms of yellow fever. Tracings from *M. rhesus* 19 on the morning of the third day of the disease. Note low voltage of R-wave and increased amplitude of S-wave in all leads: splintering of R_3; and markedly increased amplitude of T_2 and T_3.

gram of Lead I, from another animal (*M. rhesus* 12) on the morning of the third day of the disease. This event is well shown in Figs. 5 and 8. In this instance the inverted wave was followed by a P-R interval 0.008 of a second shorter in duration than the normal for that animal. This change was not found in the tracing from the same lead of the same animal on the following day. The monkey was one which showed the most marked bradycardia in the series as well as marked alterations in the T-deflection.

3. *Physiological observations upon the auriculo-ventricular bundle.*

In these experiments the time required for the conduction of the excitation wave along the A-V bundle has been an important consideration. Observations upon the P-R interval of the electrocardiogram showed that in sixteen of the nineteen animals infected with yellow

TABLE III

CONDUCTION TIME OF MONKEYS EXPERIMENTALLY INFECTED WITH YELLOW FEVER VIRUS‡

MONKEY NUMBER	NORMAL	DAYS OF INCUBATION		FIRST DAY FEVER		SECOND DAY DISEASE		THIRD DAY DISEASE		FOURTH DAY DISEASE		FIFTH DAY DISEASE		RECOVERY PERIOD
		1	3	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	A.M.	P.M.	
1	0.104				0.096	0.10	0.12	D						
2	0.088									0.10	D			
3	0.088				0.088	0.112	0.12	D						
4	0.064			0.072		0.08			D					
5	0.096		0.10	0.104		0.10	D							
6				0.06		0.08		0.08	0.08	D				
7	0.08					0.08		0.08		0.08		0.08	D	
8	0.08		0.08	0.088		0.096								
9		0.08				0.08		0.08	D					0.08
10	0.08					0.08		0.08	0.088	D				
11	0.064							0.096						
12	0.088							0.088		0.12	D			0.08
13	0.064						0.08	D						
14	0.068							0.088	0.12	D				
15	0.064				0.064*	D								
16	0.08							0.08	D					
17	0.08							0.32†	D					
18	0.064					0.08		0.08	D					
19		0.08						0.088	D					
20	0.064					0.064	0.064	D						
Control														

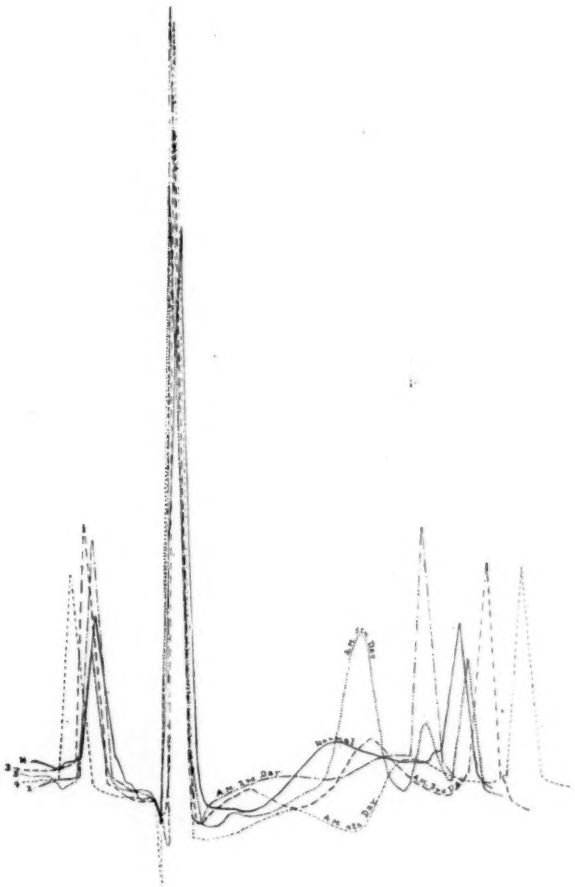
†Animal died during inscription of Lead III.

*Bled from heart, animal died.

‡As indicated by P-R interval of electrocardiogram recorded in decimals of a second.

D—Animal dead.

fever virus, there occurred prolongation of the conduction time, usually slight in degree. Moreover, with few exceptions the delay in conduction was progressive, increasing from day to day of the disease. In one of the two animals which recovered, the conduction period had



Figs. 7 and 8.—In each figure, outline drawings of a specific electrocardiographic lead from one animal are reproduced. The series of tracings composing a figure represents normal electrocardiograms and electrocardiograms taken at varying intervals during the course of the disease. The method of their preparation consisted in the projection upon a screen of lantern slide reproductions of the various electrocardiograms from a given animal. Employing always the same magnification, a representative cardiac cycle was selected in each lantern slide, and its outline was traced upon white paper. Succeeding cycles were so projected that the points of onset either of the Q- or R-waves of serial cycles were made to coincide. From this fixed point in each series the outlines were always traced. The time of annotation of each electrocardiogram is noted upon the figures. This method of illustration shows well the variations in the length of the entire cardiac cycle from day to day of the disease, variations in the duration of the P-R and R-T periods, and especially well the deformities of the R-T period and the T-wave during the course of the disease.

lessened during convalescence but at the last period of observation had not yet regained its normal time interval. It should, however, be noted that in this instance the last record was taken only four days

following the first appearance of fever. In the other recovered monkey the conduction time had returned to normal by the last day of observation. In this case the final registration was secured twenty-five days after the animal had first shown fever.

On one occasion the A-V conduction time was approximately doubled during the course of the disease. In three instances it was increased by approximately half its normal value. Just before death in one animal the P-R interval measured 0.32 of a second as contrasted with the normal period in the same animal of 0.08 of a second. Excluding from the series this one extreme value, the average greatest increase in the conduction period equalled 0.014 of a second. The

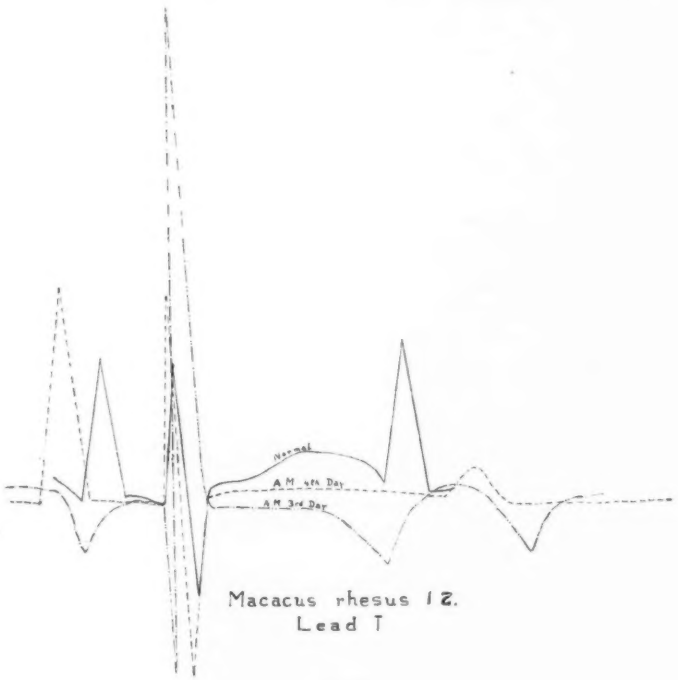


Fig. 8.

average normal value was 0.078 of a second, while the average longest period in each animal during the course of the disease was 0.092 of a second. The fact is significant that no increase in the P-R interval of the electrocardiogram occurred in the control animal dying from a peritoneal infection after a period equal in duration to the average course of yellow fever in the monkey. Table III epitomizes the detailed information regarding these variations. In Fig. 4 the P-R periods for the various animals have been plotted in graphic form, so that it may be possible to visualize the degree of the delay in conduction. The lengthening of the P-R interval on successive days of the disease is well shown in the serial cardiographic tracings (Figs. 7 and 8).

In these experiments the occurrence of altered and reduced con-

duction in the auriculo-ventricular bundle branches has been suggested in the occasional observance of definite widening of the base of the R-wave and, in one instance, of distinct notching of the apex of this deflection in a tracing taken from Lead III on the morning of the third day of the disease. That in this instance the evidence of a broadened base of R with notching of its apex is significant, is further rendered likely by the occurrence of a concurrent reversal of preponderance. At the same time T became of greatly increased height in a positive direction in all leads, while S assumed a considerably increased amplitude in Leads I and II, where it formed the most prominent "spikes" of the tracings. The several findings in the electrocardiograms from this animal are in keeping with the occurrence of a partial branch-bundle block.

Direct comparison of the conduction time with the heart rate shows in general a correspondence between the two phenomena. It has been observed that the cardiac rate of contraction decreases, while the conduction time increases during successive days of the disease. It must be noted, however, that the correspondence is an approximate and not an absolute one.

4. *Physiological observations upon the ventricular muscle.*

The study of the ventricular portion of the electrocardiogram divides itself naturally into the consideration of three groups, the QRS complex, the R-T period, and the T-wave itself.

The QRS Period.—In a review of observed alterations in the QRS portions of the ventricular electrocardiogram, the consideration of the amplitude of the different waves, except in especial instances, will be purposely avoided, because it is not believed to be a significant point. In these experiments there were very evident variations in the amplitude of the deflections from one tracing to another of the same heart at different times, both in health and during the course of the disease. The voltage of a tracing, taken on the last day of the disease, might be either higher or lower than that of the normal electrocardiogram of the same animal. That changes of amplitude of qualitative significance may occur, however, is supported by the appearance of certain alterations of unusual incidence associated with other and more significant changes. An S-wave, previously absent or poorly defined in Lead III, has during the course of the disease been observed to become of considerable amplitude, and in association with a diminution in the size of R, to assume the place of the most prominent "spike" in the tracings. Similarly S, a badly demarcated wave in Leads II and III of the electrocardiograms taken before inoculation of the animal with yellow fever virus, has been seen to become of marked amplitude with a diminution of the R-wave in the same leads on the later days of the disease (Fig. 6). Not infrequently a Q-wave barely discernible in Lead I of the normal tracing had attained so great an amplitude, in

later stages of the disease, as to appear as the most prominent "spike" in the electrocardiogram from the same lead. Changes in preponderance from day to day of the disease have been commonly noted. A splintering of the R-wave in Lead III has been found associated with variation in the amplitude of the associated deflections of the ventricular electrocardiogram (Fig. 6).

The R-T Period.—A much more definite change observed in the ventricular electrocardiogram during experimental yellow fever resembles changes of similar form described by Pardee[49] as evidence of blocking of a branch of the coronary artery, and by Cohn and Swift[11] as well as Rothschild, Sacks, and Libman,[54] as occurring in the acute phases of rheumatic fever. This change consists in deformity of the R-T or S-T period of the electrocardiogram. A significant deviation of this portion of the electrocardiogram is that which occurs when the downstroke of the R-wave fails to reach the base line, but instead commences abruptly upon a curve, convex upwards, occupying the entire R-T period, and becoming finally incorporated in the upstroke of the T-wave, so that it appears that the latter is given off directly from the R-wave. In other instances and even in the same tracing, the descending limb of the R-wave may extend below the line of equipotential to form a rounded S-wave, when the R-T segment, instead of occupying an almost horizontal position, may slope upward or downward to form an acute angle with the horizontal base line, and to merge itself gradually without appreciable distinction into the T deflection, thus imparting to the latter a diphasic appearance. While these two types of deformity of the R-T segment of the electrocardiogram represent changes typical of the later stages of experimental yellow fever, no specificity is attached to them, nor is it implied that these changes are of most frequent occurrence. They represent rather the more definite types of alteration among a series of changes comparable to them, which differ from them only unimportantly in their contours, and which exist with them in the same electrocardiographic series and even in the same tracing. The serial electrocardiographic tracings (Figs. 7 and 8) show clearly this pleomorphism in the contour of the R-T period in the electrocardiograms of yellow fever.

Observations upon the length of the R-T interval showed that in eighteen of the nineteen animals studied electrocardiographically during the course of infection with experimental yellow fever, an increase was noted in the duration of this period. The prolongation of the R-T interval was progressive in character and increased from day to day of the disease. There was in general a parallelism in the progressive increase in length of the R-T period with that of the R-R period, but the relation was by no means a constant one. While the ratios between the durations of the two periods showed in many instances an approximate correspondence, in others they presented wide divergence. In three experiments, lengthening of the period became so

marked that T encroached on the following P-wave or else the latter became superimposed on the T deflection. The control animal suffering from an infection of the peritoneum also presented a lengthening of the R-T period. The only animal in this series which did not show lengthening of the R-T interval recovered from the disease. The other recovered animal presented prolongation of this period during the course of the disease, with subsequent shortening during convalescence. In the light of our present knowledge of electrocardiography, it is impossible to determine the significance of the lengthened R-T period. The lengthening of the period is also shown in Figs. 7 and 8.

The T-wave.—The results of the study of the T-wave of the electrocardiogram in experimental yellow fever reveal certain observations which are significant because of their frequency and uniformity of occurrence. These changes warrant consideration. It has been noted that in fourteen of the nineteen animals infected with yellow fever virus, the character of the T-wave became altered in the end stages of the disease, becoming in one or more leads either diphasic, reduplicated, negative, or accentuated in its inscription. These deformities of the T-wave were independent of alterations in the initial ventricular deflections (QRS complexes). The normal upright terminal wave of the ventricular electrocardiogram was inconstantly replaced by a deflection either negative in direction, or diphasic in contour, the latter presenting either two waves above the line of equipotential or one positive and one negative wave in relation to the base line (Figs. 5, 7, 8). Exclusive of these types of deformity of the terminal deflection, an upright T-wave of increased height associated with other electrocardiographic changes has been a common finding (Fig. 6). An accentuated terminal deflection has, however, been observed upon two occasions in tracings from normal animals.

Two of the five animals (*M. rhesus* 8 and *M. cynomolgus* 11) which failed to show alterations in the T deflection recovered from the disease. The remaining three animals were not fairly representative of the course of the experiment, as each died prematurely of early or only moderately advanced yellow fever lesions, hastened in their death in two instances (*M. rhesus* 1 and 3) by the coma and subnormal temperature induced by the administration of sodium iso-amyl-ethyl-barbiturate, and in a third (*M. rhesus* 15) by the loss of blood following a cardiac bleeding. Nevertheless, even with these animals included in the series, the incidence of aberrant T deflections is a noteworthy one, occurring as it did in 74 per cent of the monkeys dying of yellow fever. A study of the time relationship of these changes to the course of yellow fever reveals the fact that the abnormal variations appeared most frequently on the latter days of the disease. In nine of the thirteen animals in which they were observed, these alterations were first noted on the day of death. In five of these nine cases it had been

possible to obtain tracings on the monkeys on the day previous to death; the electrocardiograms taken on this day showed normal T deflections. In two animals the abnormal waves were first inscribed on the day preceding death and in one they were first noted two days previous to the animal's death. In seven of the fourteen instances in which significant alterations in the T-waves existed, negative deflections were observed in either Lead I or Lead II, or in both of these leads (Fig. 5). This fact is pointed out not because it is believed that the negative variations were the most significant of those noted, but rather because in a purely empirical way we know most about this type of change in the T-wave. Before leaving the consideration of the terminal portion of the ventricular electrocardiogram in yellow fever, it is important to note the ephemeral character of any given deformity either of the R-T period or of the T-wave. These disturbances are transient, fleeting in nature, present in one tracing and not in another, one type of variation being inscribed upon one occasion, and a different deformity appearing during subsequent inscriptions. The variations of the T deflections and of the R-T period during the course of the disease are well represented in the serial electrocardiographic tracings (Figs. 7 and 8).

DISCUSSION

A perusal of the literature upon bradycardias of sino-atrial origin engenders the belief that those types of sino-auricular block which are invariably associated with irregular or inconstant forms of bradycardia, and which occur in relatively normal hearts, possess nothing in common with the retarded heart rate of yellow fever. That a relationship may exist between some types of the so-called sino-auricular block and the bradycardia of yellow fever, is, however, rendered problematical in view of the observations of Mackenzie[45] and Riebold.[50] The former author first described the condition as occurring in influenzal myocardial involvement, and suggested "that the heart symptoms in this case, and it may be in the slow irregular hearts in diphtherial cases, are due, not to vagus stimulation but to a poison acting like digitalis, directly on the heart itself." Riebold also expressed the belief of a relation of sino-auricular block to infectious diseases. More recently Cohn and Swift[11] have reported the occurrence of sino-atrial block in the course of rheumatic fever; and Smith[60] has recorded its incidence in diphtheria. A type of sinus bradycardia closely resembling that of experimental yellow fever, has been reported by Winternitz and Selye[68] as a result of thrombosis of the artery to the sino-atrial node.

In the consideration of the relation of jaundice to the slow cardiac rhythm of yellow fever, certain observations are of value. The fact is so well known that bradycardia is frequently a concomitant manifestation of the icteric state that a second fact needs to be empha-

sized, namely, that the association is by no means a universal one.[51, 67, 6] Every experienced observer has seen numerous cases in which the most marked degrees of jaundice were accompanied by a rapid pulse. The facts that a retarded cardiac rate is a constant phenomenon in experimental yellow fever, and that jaundice is very inconstantly associated with slow heart action, offer an inconsistency which militates against the possibility of a causal relationship of the icterus to the bradycardia in this disease. The bradycardia associated with icterus is of an irregular type,[67] whereas that of yellow fever is a regular one. Moreover, in yellow fever bradycardia may occur independently of jaundice, and in the presence of a normal bilirubin content of the serum.[4]

The hypothesis which Chagas has advanced that the bradycardia of yellow fever is a part of a "suprarenal syndrome" fails to attain credence in consideration of the fact that in the two cases in his series in which suprarenal lesions were found at autopsy the degeneration was confined to the cortical zones.[61]

In the auricular electrocardiograms of yellow fever, the occurrences of reduplicated and more especially of inverted P-waves, though infrequent, are of importance. A negative P-wave has been regarded by many workers[31, 32, 52, 47, 25, 65, 66, 7, 23, 13] as indicating a shifting of the pacemaker from its normal position in the upper extremity[40] of the S-A node to a lower functional level in the sinus node, auricle or A-V node. Negative P-waves can be produced experimentally in the tracings taken from animals during vagus stimulation, in which instance they may be abolished by atropine.[27, 17, 24, 26, 18] In some cases, however, negative P-waves persist after atropinization, and do not change on compression of the vagus nerve in the neck.[7] Wiggers[64] believes that in these instances, the sino-atrial node should not be thought to be the seat of disease, unless the inverted waves are associated with a reduced or a reversed P-R interval, or are accompanied by auricular extrasystoles or periodically give rise to tachycardia.

The lengthening of the P-R interval of the electrocardiogram, moderate in degree, which has been observed with considerable constancy during the course of experimental yellow fever, is indicative of an impairment of function in the auriculo-ventricular bundle.

In experimental yellow fever the changes in the ventricular electrocardiogram are of especial interest. Because of the considerable amount of evidence which has been obtained in recent years relating to alterations in the T-wave of the electrocardiogram, which have been observed during the course of many disease conditions provocative of damage to heart muscle, it is important that we should consider the changes in the terminal deflections which have been so frequently encountered during the course of experimental yellow fever. The observations on the latter disease are of singular significance in that in this instance the opportunity has been afforded of correlating these func-

tional aberrations with the findings of histopathology in the precise muscular tissue in which they were produced only a few hours antecedent to the fixation of the tissue. This privilege obtains only in a few diseases, and in still fewer may the study be conducted under the more readily controlled methods of animal experimentation. Observations relating to the histopathological changes in the myocardial tissues in this series of animals will be published in another paper.

General acceptance is accorded the view that the initial portion of the ventricular electrocardiogram, the QRS complex, represents a composite tracing of the differences in electrical potential set up in the plane of the lead by the wave of excitation passing throughout both ventricles.[41, 33, 34] The period between R and T or between S and T, which in the normal electrocardiogram usually follows the base line, indicates an electrical equilibrium in the cardiac musculature in the plane of the lead at that time, and implies that a state of excitation exists throughout the ventricles. The frequent divergence of this portion of the curve in yellow fever suggests a disturbance of those stresses which normally during this period repose in equilibrium.

In view of our present information upon this subject, no justification exists for attaching a specific significance to a single form of alteration in the contour of the end deflection. The occurrence of one type of deformity of the T-wave at the time of registration of a given lead, and of another deformity in the same lead at another time of recording during the progress of the disease, suggests a common basis for these aberrations and an existing relationship between them. Rosnowski[53] has noted the occurrence of changes in the end deflection in the course of intoxications which, like yellow fever, result in diastolic arrest of the ventricles. The common observance of the markedly accentuated T-wave with a high, sharply vertical summit during the later days of the disease may, with caution, be tentatively accepted as a deformity of the terminal deflection of undetermined significance. There is no evidence of a different pathological interpretation of a T-curve which is diphasic in contour from one solely negative in direction. The incidence of abnormal deflections in more than one lead from the same animal, and their occurrence in the first and second leads, would seem to be more important than a solitary incidence of the change, especially if the latter presented itself in Lead III alone. In the extent of existing knowledge it is only justifiable to attribute to these T deflections of proved altered and abnormal contour, whether they be inverted, diphasic, or doubly positive in direction, the general significance of an abnormal retreat of the excitation process. They are signs that the myocardium is not behaving normally.

The consideration which the presented observations make desirable of emphasis is that well-marked deformities of the T-wave, such as are never observed in the healthy animal under the conditions of the experiment, are recorded with considerable constancy of occurrence

on the latter days of the disease, at a time at which subsequent observations have shown that advancing myocardial degeneration is taking place in the ventricles. For these reasons the suggestion is advanced that alteration in the end deflection of the electrocardiogram may afford valuable information of functional injury to the ventricular muscle. This concept is further supported by the fact that alterations in the T deflection were absent in the two animals in the series studied which recovered from the disease, while they were present in all the monkeys which died, with uncomplicated lesions of yellow fever, at the end of a complete course of the infection. The deformities of the T-wave were also not observed in the animal dying from peritonitis at the end of a comparable period.

SUMMARY

1. Bradycardia, regular in rhythm, absolute in degree, and progressively more marked on succeeding days of the disease, has been a constant finding in experimental yellow fever in the monkey; the phenomenon persisted independently of ether anesthesia, sodium isoamyl-ethyl barbiturate anesthesia, and bilateral section of the vagus nerves.

2. Reduplication of the P-wave of the electrocardiogram was occasionally observed in experimental yellow fever; more rarely this deflection was seen to be inverted.

3. Prolongation of the conduction time of the auriculo-ventricular bundle was observed in slight or moderate degree in 84 per cent of cases.

4. Among electrocardiographic alterations referable to the ventricular muscle during the course of the disease, changes in ventricular preponderance were commonly observed. The R-T period was lengthened in 94 per cent of cases; and frequently it was deformed. The normal upright T-wave was replaced in 74 per cent of cases by a deflection either negative in direction, diphasic in contour, or increased in height.

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THE MYOCARDIUM IN YELLOW FEVER

II. The Myocardial Lesions in Experimental Yellow Fever*

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INTRODUCTION

IN A PRECEDING paper in this Journal the myocardial function registered by electrocardiography in rhesus monkeys during the course of experimental yellow fever, has been described. In this communication it is desired to present the evidence of histopathological alterations in the myocardial tissues of the group of animals upon which electrocardiographic tracings were obtained, supplemented by the results of the study of tissues from other animals in which the heartbeat had not been recorded during the course of the disease. Finally, it is hoped in some degree to correlate the graphic records of the disturbances of the heart action with the findings on microscopic examination of the tissues in which the disturbances arose.

The examination of numerous reports and descriptions of the gross and microscopic pathological conditions of the heart muscle in yellow fever reveals a remarkable discrepancy of observation and opinion. The conflicting evidence can be explained in part by the fact that all observers were not studying yellow fever. In addition to this consideration, the intensity of the lesions has undoubtedly varied in different epidemics and in individual cases.

Sodre and Couto,[17] in 1901, observed the occurrence of hemorrhagic foci in the heart muscle, pericardium, and endocardium, noting as well the flabby condition of the myocardium in yellow fever. The aortitis and endocarditis which these authors described must be regarded as evidence of either antecedent or secondary infection. Microscopically, they found a patchy, fatty degeneration of the muscle fibers, occasional loss of cross striation in the sarcoplasm, and irregularity of size, form, and staining reactions of the nuclei.

In 1905 Otto and Neumann,[14] and later Otto,[13] described the heart muscle in yellow fever as showing all stages macroscopically from cloudy swelling to fatty degeneration. Microscopically, they observed a well-marked though delicate, irregularly distributed, fatty degeneration of the fibers; but these changes were less marked than those which they expected to observe from the consideration of the macroscopic appearances of the muscle.

The following year Marchoux and Simond[12] in their study of the dis-

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ease noted only a slightly marked fatty degeneration of heart muscle, which though it affected some fibers, left others, in their opinion, in a nearly healthy state.

In 1912 Rocha Lima[15] described the myocardium in yellow fever as soft and clay-colored, presenting microscopically the occurrence of more or less extensive, irregularly distributed granular and vacuolar degenerations. The nuclei of the muscle fibers were always well stained but often of conspicuously large dimensions. The muscle fibrillae and cross striations were constantly clearly discernible.

During this period Seidelin,[16] writing of the pathology of yellow fever, reported the condition of the heart muscle in the disease as macroscopically pale or irregularly streaked or spotted in color, and diminished or friable in consistency. Histologically a fatty metamorphosis of the fibers could be observed.

Elliott,[6] in 1920, noted loss of nuclei and cross striations in the most severely damaged muscle fibers. Six years later Aitken and his coworkers[1] recorded the occurrence of vacuolization in the myocardial fibers.

In 1927 Klotz[10] described the changes in the heart muscle in yellow fever as degenerative ones unaccompanied by inflammation and affecting the myocardium in all its parts, including the auriculo-ventricular conducting system. Dilatation of the left ventricle was not uncommonly observed, and the muscular walls were soft and flabby as a result of granular and fatty degenerative changes in their substance.

A year later Cannell[5] recorded accurately in *Homo sapiens* and *Macacus rhesus* the patchy and irregular distributions of the fatty and granular degenerations, noting that in each fiber the former change was most marked about the nucleus. The pathological findings were essentially similar in the two species. Degenerative changes were present in both the ordinary myocardial muscle and the auriculo-ventricular bundle.

Contemporary with Cannell's observations, Hudson[9] reported the occurrence of an irregularly distributed fatty degeneration of the cardiac fibers in monkeys experimentally infected with yellow fever, but found little change of cellular structure in the study of ordinary paraffin sections. The occurrence of congestion and less often of hemorrhage in the myocardial capillary bed was noted by the latter author.

In 1929 Fialho,[7] describing the pathological findings in the recent epidemic of yellow fever in Brazil, noted pericardial and endocardial hemorrhages, dilatation of the right ventricular cavity, and fatty degeneration of the muscle. He believed the fatty change to have been more marked on the right side of the heart.

TECHNICAL METHODS

Selection of Material.—The material utilized for histopathological study consisted of the myocardial tissues of nineteen animals studied electrocardiographically

during infection with yellow fever virus, and of blocks of heart muscle from fourteen other monkeys, in which the myocardial function had not been examined during the course of the disease. A study of sections of liver, kidney, and spleen in these animals verified the existence of yellow fever. As a control to the investigation of the cardiac histopathology, comparable tissues were examined from four animals studied electrocardiographically as controls in vagotomy experiments, as well as blocks from various regions of heart muscle from five other healthy rhesus monkeys. As an adjunct to this study and for purposes of comparison, the myocardial tissues were examined from cases of acute yellow atrophy of the liver, eclampsia, and diphtheria in man.

Selection of Blocks.—All the blocks of heart muscle taken from the animals examined electrocardiographically were fixed in Zenker's fluid. Of the remaining yellow fever and control animals, some tissues were fixed in Zenker's fluid while others, in order to offer a greater breadth of study, were fixed in a 10 per cent formalin solution. Blocks of tissue were excised from these hearts in four representative regions, the sulcus terminalis region of the superior caval-auricular junction, the upper ventricular and lower auricular septal region, including the membranous portion and septal curtains of the tricuspid and aortic valves, and longitudinal areas of the musculature of the right and left ventricles. In special instances, in both diseased and healthy hearts, large blocks of the septum were cut out to include the coronary sinus region posteriorly and the anterior border of the membranous septum anteriorly. Serial sections taken through such blocks offered an opportunity for study of the auriculo-ventricular node and the crus commune of the auriculo-ventricular bundle at various levels of its course.

From blocks of tissue including the superior caval-auricular junction serial sections were cut from above downward in a plane at right angles to the course of the superior vena cava through the region of junction of that vessel with the musculature of the right auricular appendix. The sino-atrial node was invariably demonstrable in these sections situated deeply to the sulcus terminalis, as a well-defined, crescent-shaped group of fibers situated subendocardially, coursing around the caval mouth for a distance of 2.5 mm. on its right anterolateral aspect. Serial sections, taken through the greater part of the depth of the node, were prepared from twenty-seven monkey hearts. In this group there were five control series, eighteen series of paraffin sections from yellow fever hearts showing slow cardiac rate of beating during life, one series from an animal studied electrocardiographically during infection of the peritoneum, one series from an animal dying prematurely due to operative cardiac bleeding, and three series of frozen sections from yellow fever animals not studied electrocardiographically.

The auricular muscle was examined in microscopic preparations from twenty-nine monkey hearts. In this group there were twenty-seven series of paraffin sections and two series of frozen sections. Six control and twenty-three yellow fever animals are represented in the group.

The condition of the auriculo-ventricular bundle was investigated by the method of serial section in five yellow fever and three control animals. Sections of diseased and control tissues were compared from level to level through the course of the bundle. This method of study is of considerable importance in any investigation of the histopathology of the auriculo-ventricular bundle, because of changing cytological characters in the component cells, as the fibers of the crus commune course from the region of the auriculo-ventricular node to the forking of the bundle stem. Vacuolization and a loosely granular cortex are histological findings which ought to be regarded as normal in the latter region, whereas their occurrence in the former should excite the suspicion of degenerative change. With these considerations in mind, sections of control and diseased tissue from approximately the same levels have been compared in this study.

Blocks for section were taken from the ventricular musculature, both right and left, of forty hearts. In this series the tissue was obtained from thirty-six monkeys dying of yellow fever and from four healthy animals of the same species.

Methods of Staining.—Paraffin sections of the sino-atrial node, auricular muscle, auriculo-ventricular bundle, and ventricular muscle were stained by various methods, of which the hematoxylin and eosin and phloxin-azure B. methylene blue technics were most frequently employed. Less often special sections were stained by iron hematoxylin and eosin, the Giemsa stain, or Mallory's orange-G methylene blue connective tissue stain. Frozen sections cut from each of these regions were stained for fifteen hours in Sudan III.

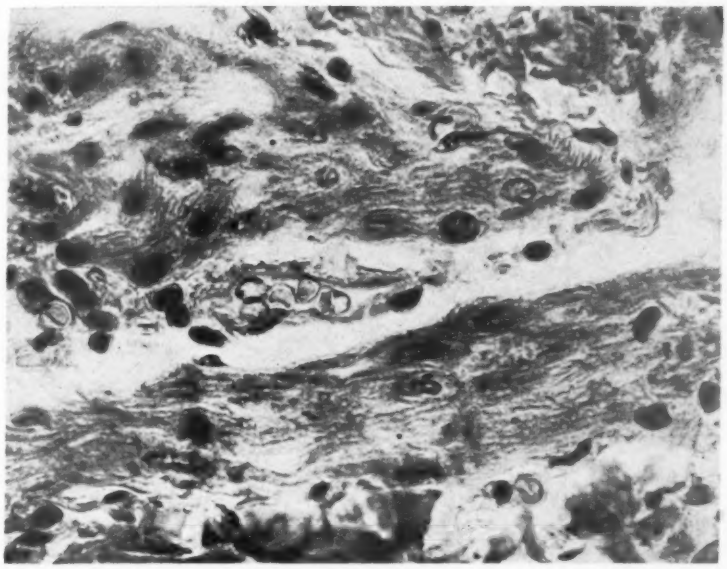

Fig.1.—Sino-atrial nodal musculature in yellow fever. The darker areas along the course of the fibers represent areas of hyaline change. In intervening areas the protoplasm appears rarefied. In several fibers karyolysis has resulted in loss of nuclei. (Hematoxylin and eosin.)

RESULTS

1. *Histological observations on the sino-atrial node.*

The microscopic preparations of the sino-atrial node from animals dying of yellow fever presented histopathological changes both in the sino-atrial muscle and in the ganglion cells in proximate or immediate relation with the muscle fibers. In paraffin sections two different types of alteration were noted in these fibers. A patchy, hyaline-like change of the specialized muscle fibers, irregular in distribution and present as a splash-like accentuation of the acidophilic dye in any field, was the characteristic of the first type of lesion (Figs. 1 and 2). Areas of cytoplasm in these cell groups were deeply acidophilic staining, but coarsely granular in consistency and less refractile than in true hyaline change. The hyaline-like appearance was not uniform over any one patch, varying in its intensity of staining from one cell to another, and even from one part of a fiber to another part. Karyolysis in these cells

was not infrequently observed, and pyknosis was of relatively common occurrence. Irregularly shaped nuclei and occasionally empty ones indicated early stages of karyolysis. The other type of change encountered in the nodal muscle fibers was characterized by karyolysis of nuclei, vacuolization of cytoplasm, and loss of cell boundaries (Fig. 2). It was even more irregular in its distribution than the first type of structural alteration. Scattered areas showed almost complete myolysis of cells, while intervening areas were left relatively intact. Vacuolization was represented in some cells by numerous, nonstaining areas 3 to 4 μ in diameter. In other fibers the faded nucleus might be observed suspended freely in a completely vacuolated cell, in which only a thin strip of cortex remained; acidophilic degeneration of the karyoplasm

Fig. 2.—Sino-atrial nodal musculature in yellow fever. The heart rate of this animal (*M. rhesus* 12) was reduced to a third of its normal value during the course of yellow fever. The darker areas along the course of the fibers are areas of hyaline change. Vacuolization of fibers is also well shown. (Phloxin and azure B methylene blue.)

was a common nuclear change, and many nuclei were large, swollen, and hydropic in appearance. In what would seem to be the earlier stages of this process, the cytoplasm of the nodal cells appeared swollen, and composed of fine granules, which were palely staining and greatly dispersed. A fraying or fibrillation of the sarcostyles was a common finding. Cross striations in these fibers were usually lost, but in a few instances they were accentuated. In the later stages of this change, occasional cells appeared only in skeleton outline, with acidophilic cytoplasmic granules remaining interspersed between frayed myofibrillae. Cellular infiltrations were very rarely noted, and then only as sparse perivascular collections of lymphocytes. In some of the hearts examined

in this study actual necrosis of ganglion cells was observed. Many fields could be found in which two or more of these cells had been completely destroyed, with only the space previously occupied by the ganglion cell, or a cobweb-like network of palely staining cytoplasm, remaining. In the intermediate period leading to this complete lysis of nerve cells, the appearances of different cells suggested that both nucleus and cytoplasm had passed through successive stages. In the beginning the nucleus seemed to swell, at first somewhat disproportionately, its nuclear membrane becoming paler and less distinctly demarcated. At this stage the nucleolus could be observed as a palely staining oval disc colored a robin's egg blue by basophilic dyes and occupying

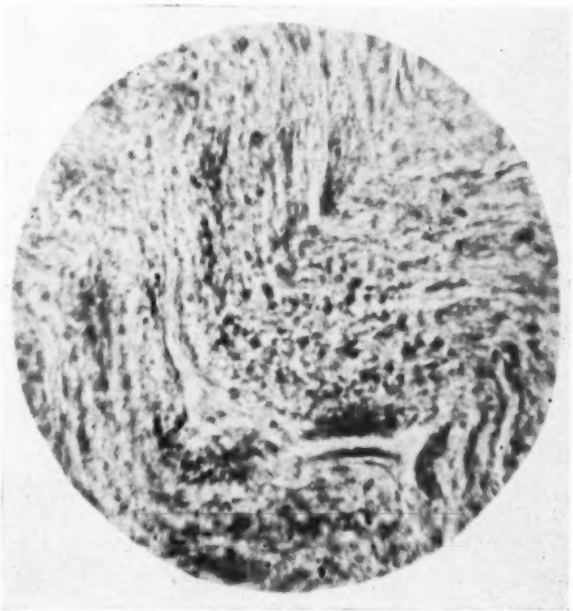

Fig. 3.—Sino-atrial nodal musculature in yellow fever. (*M. rhesus* 25.) Droplets of neutral fat, appearing as darkly shaded globules in the figure, are seen irregularly distributed in many fibers. (Sudan III and hematoxylin.)

the approximate center of the nucleus. About the nucleolus the chromatin structure first became altered both in form and in staining reactions. The normal appearance of a chromatin network and its grouping of particles became lost, and a greater or lesser aggregation of the latter, composed of pieces of chromatin grading down in size from a diameter one-eighth that of the nucleolus to the point of visibility, could be observed clustered together and apparently overlapping and fusing with each other. These particles gradually lost their affinity for basophilic dyes; they became colored by acidophilic stains, for the most part rather intensely. In later stages the aggregations of chromatin became chiefly grouped about the nucleolus, but smaller collections could be observed beneath the nuclear membrane; the intermediate nuclear zone was left

comparatively unoccupied. In the end, the nucleus frequently existed only as an oval vacuole containing loosely granular débris. Sometimes it appeared as a large oval disc, no longer possessing the sharply outlined border of the nuclear membrane but made up of dense, closely packed, coarsely granular, deeply staining, acidophilic, karyolytic débris. Concomitant changes in the cytoplasm were manifested by its substance becoming more coarsely granular. In some areas it acquired a purplish flush, losing its homogeneous mauve in phloxin and methylene blue preparations. Later there appeared areas of nonstaining or very palely staining protoplasm eteling away its substance until the cytoplasm remained only as a vastly vacuolated cobweb-like structure. These changes which have been described in nodal muscle fiber and ganglion cell are the positive findings, the end picture of a varying degree of change which in different hearts progresses from a state which appears to deviate little from the normal. The nodal muscle fibers stained with Sudan III showed an irregular and patchy fatty degeneration (Fig. 3). While some fibers were very nearly free of fat, most cells contained a varying quantity. Many fibers presented large amounts of neutral fat in which the component droplets were for the most part of relatively large size; the size of these droplets ranged from 0.4 to 4 μ in diameter. Differing considerably in their size, the droplets varied much more in their distribution. They were usually largest and most numerous about the nucleus. The globules of fat tended to be arranged in parallel columns. Larger droplets appeared to have been formed by the coalescence of smaller ones. Some groups composed of twenty or thirty fibers were involved together in extreme fatty change in which 50 per cent or more of the total cell volume appeared to be occupied by neutral fat. The amount of fat was greatly in excess of the occasional dispersed fine granules which can sometimes be demonstrated normally in these fibers by the same technic. The ganglion cells showed occasional fat droplets in their cytoplasm.

The degenerative changes present in the nodal muscle fibers in the hearts of animals dead of yellow fever were at all times so marked that observers skilled in histopathology, examining unidentified microscopic preparation, were able to distinguish sections prepared from animals that had died from yellow fever from those obtained from control animals. Examined in this unprejudiced way, the sections which presented the most advanced lesions were found to have been taken from hearts which showed the most marked degrees of bradycardia during the course of the disease. In the nodal tissue from a monkey dying of a peritonitic infection there was a notable absence of degenerative changes.

2. *Histological observations on the auricular muscle.*

The alterations noted in the auricular muscle fibers were in no way different in character or degree from those observed in the specialized musculature of the node. When cut in cross-section the auricular mus-

cle fibers showed frequent perinuclear vacuolation and not uncommonly, loss of nuclei. Viewed in this way the cytoplasm of the cells presented a curious coarsely granular appearance because the cortices were composed of relatively large, deeply staining, loosely dispersed sarcoplasmic elements. In longitudinal section not only was perinuclear vacuolation well demonstrated, but vacuoles were frequently evident in other portions of the cell. The fiber itself usually exhibited a swollen hydropic appearance, and its outline was frequently less well demarcated than in normal tissues. Cross striations were rarely accentuated; more commonly they had become indistinct or quite lost. Fibrillation, unequal fraying, and disruption of the myofibrillae were commonly noted. When these processes reached extreme degrees in isolated cell groups, they

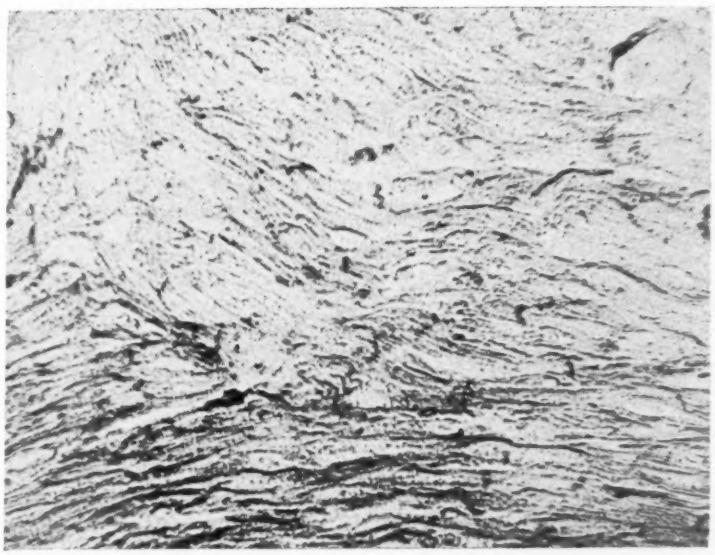

Fig. 4.—Auricular musculature in yellow fever. (*M. rhesus* 12.) Note vacuolization of protoplasm and karyolysis of nuclei. (Phloxin and azure B methylene blue.)

appeared as areas of myolysis. Sparse infiltrations of mononuclear leucocytes were only occasionally encountered. In addition to granular and vacuolar types of degeneration, a patchy hyaline-like change of the auricular fibers was frequently observed. In many instances this alteration affected whole cells but in its most typical form it was present as a transverse acidophilic "barring" of the longitudinally coursing muscle fibers. Such an appearance was imparted to these cells by an alternate patch-like accentuation of the acidophilic staining along the course of the fiber. Nuclear alterations were manifest in the common occurrence of pyknosis, while karyolysis was frequently observed in the areas of muscular degeneration and myolysis. In the cells of such areas the lysis of nuclei presented many and diverse forms, varying from swollen ones of distorted and irregular contour and watery ap-

pearance to nuclei disrupted and remaining only as acidophilic granular débris. In sections stained with hematoxylin and Sudan III, fat was observed to be present in relatively large quantities in the auricular muscle. The fatty degeneration, in common with the other types of cell injury, was irregular in its distribution from fiber to fiber and unequal in its quantity within each cell. Granular, vacuolar, and fatty degeneration with the rarer myolysis of cells are descriptive terms which represent the kind of picture which the lesion presented in different instances, and with the employment of various staining methods (Fig. 4).

3. *Histological observations on the auriculo-ventricular bundle.*

Sections of the crus commune of the auriculoventricular bundle stained with hematoxylin and eosin showed a patchy, hyaline-like change

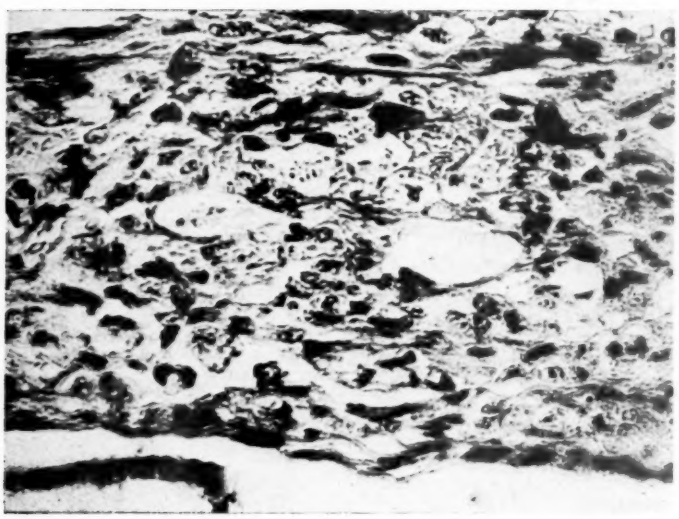

Fig. 5.—Auriculo-ventricular bundle in yellow fever. (*M. rhesus* 26.) Note vacuolar degeneration of protoplasm and karyolysis of nuclei. (Phloxin and azure B methylene blue.)

of many fibers. The cytoplasm of others was more coarsely granular than in normal control sections. Pyknosis was a common event, and karyolysis of nuclei was not infrequently encountered. More marked changes were occasionally met with in the bundle tissue. Once hemorrhage among the component cells was observed. When the fibers of the crus commune were studied in sections stained with iron hematoxylin and eosin, phloxin and azure B methylene blue, and Giemsa stain, the histopathological alterations became much more apparent than in sections stained with hematoxylin and eosin. Myolysis of small cell groups gave an appearance of etching away of portions of the bundle stem (Fig. 5). The nuclei of these degenerating cells frequently presented a swollen and hydropic structure, associated with fragmentation of the chromatin network. The staining qualities of the karyoplasm

became altered and more acidophilic in character with the progress of nuclear injury. Clumps of chromatin were conspicuous in these nuclei because of their size, bizarre form, and brilliantly acidophilic coloration. Frozen sections of the auriculo-ventricular bundle stained with Sudan III, demonstrated the presence of neutral fat in pathological amounts and distribution. The size of the droplets varied, but they were for the most part minute though numerous. The quantity of fatty change differed from area to area; in each cell the fat globules were usually most numerous about the nuclei. Sections of the auriculo-ventricular bundle prepared from healthy rhesus monkeys and treated by the same method of Sudan III staining, showed an absence of demonstrable fat in the specialized musculature. That special staining methods will

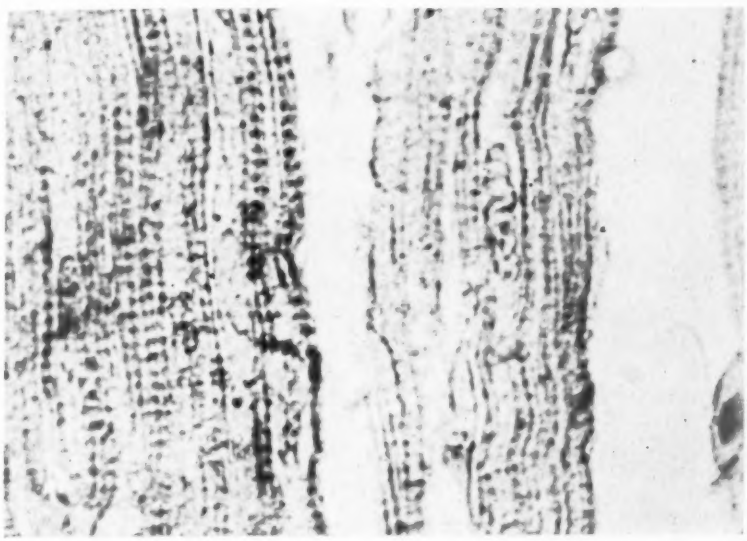

Fig. 6.—Ventricular musculature in yellow fever. (*M. rhesus* 13.) Note granular and vacuolar degeneration of protoplasm. This animal presented deformities of the ventricular electrocardiogram during the course of the disease. (Hematoxylin and eosin.)

permit the demonstration of fat in the normal auriculo-ventricular bundle[4] and in the normal myocardium[2, 3] has, however, been well demonstrated by Bullard. In the latter instance, the distribution is a much more uniform one than is encountered in disease.

4. *Histological observations upon the ventricular musculature.*

In sections of ventricular muscle both cross and longitudinal striations were frequently observed to be lost over wide areas. More rarely were these markings accentuated. The protoplasm of the fibers was coarsely granular, while perinuclear vacuolation was of common occurrence. The granular components of the cortices of these cells were rather widely dispersed beneath a swollen sarcolemma (Fig. 6). A patchy, glossy, hyaline appearance of portions of the fiber length, al-

ternating with more faintly staining areas, was frequently encountered. In many places cell outlines were lost, and nuclear degeneration forms were encountered in every field. Many nuclei were of irregular contour and pyknotic appearance. Not a few were seen to be swollen, surrounded by a thinned and stretched nuclear membrane, filled by a watery karyoplasm. A peculiar and rather definite type of karyolysis, more marked and elaborate in degree than anything of the sort observed in acute yellow atrophy or eclampsia, is worthy of mention. The train of events suggested by the process of nuclear destruction is that of a nucleus, at first swollen, of uniform or irregular contour, the chromatin network of which becomes first fragmented, then dispersed, and lastly clumped, at first basophilic, later amphichromatic, finally acidophilic and pale, the etching of its former self, transmogrified in rose-colored relief, in the perinuclear lacuna of a degenerated cell. Special fat staining of the ventricular muscle fibers demonstrated the occurrence of numerous globules, variable in number, patchy in distribution, linear in arrangement, and perinuclear in concentration, as had been observed in other parts of the myocardium.

DISCUSSION

On the basis of much physiological and anatomical knowledge there has developed a concept, fundamental to modern cardiology, that a bradycardia affecting the whole heart finds its origin in change of vagus nerve or sino-atrial node. In the experiments here recorded it has been shown that reduction of function in the vagal fibers to the heart by the administration of ether[8] or by anesthesia with sodium iso-amyl-ethyl barbiturate,[11] or the abrogation of this function by bilateral section of the vagus nerves has no significant effect upon the slow heart action in experimental yellow fever.

The study of serial sections of the sino-atrial node in animals which presented a slow heart rate during the course of their infection with yellow fever has afforded us evidence of a positive nature. In this structure degeneration of the specialized nodal muscle fibers has been observed varying in degree and most marked in the cases presenting the slowest heart rates during life. Coexistent degenerative changes in the ganglion cells in contiguous or proximate relationship to this musculature, which might conceivably affect postganglionic vagal fibers, have also been noted. Although the proof cannot be absolute in the state of our present knowledge of the relation of myocardial injury to the evolution and determination of heart rate, it seems probable that the lesion of the sino-atrial tissues is responsible for, or closely related to, the production of the bradycardia of yellow fever.

Apart from the sino-atrial musculature, alterations in the auricular muscle proper have been noted by both physiological and histological methods during the course of experimental yellow fever. With the

changes observed in the auricular muscle by electrocardiographic methods may be correlated the alterations in this tissue revealed by histopathological studies. Pursuing a parallel course with the deformities of the P-wave, suggestive of a functional disturbance in the auricular muscle perhaps attended by a depressed function of the sino-atrial node, degenerative changes, varying in degree in different instances, have been manifest in the corresponding tissues. Occasionally small hemorrhages have been encountered in the auricular wall. In view of these concurrent alterations in form and function it seems reasonable to consider as a part of the myocardial degenerations of yellow fever an auricular degeneration which is associated with functional injury to atrial muscle, occasionally manifested by evident changes in the auricular electrocardiogram.

In the isolated auriculo-ventricular bundle we are afforded the opportunity of studying a portion of the myocardium which graphic, and histological methods enable us to delineate with a degree of accuracy unusual in biological investigation. Many observations during the past thirty years have definitely established the auriculo-ventricular bundle in the mammalian heart as the muscular link responsible for the conduction of the wave of excitation from auricle to ventricle. The lengthening of the P-R interval, moderate in degree, which has been observed with considerable constancy in the electrocardiographic records of experimental yellow fever in the monkey, may be considered as a sign of impairment of function in the auriculo-ventricular bundle. The histopathological examination of the junctional tissues presenting such evidence of functional impairment has demonstrated the presence of clearly demarcated degenerative changes. The pathological basis of impaired conduction has been found in a degeneration of the muscular fibers of the auriculo-ventricular bundle, which thus altered by the disease may present the appearances of granular, fatty, hyaline, vacuolar, or myolytic change.

The occurrence of degenerative lesions in the ventricular musculature in experimental yellow fever becomes an important consideration in view of the fact that functional disturbances in this tissue during the course of the disease were provocative of deformity of the R-T segment and inversion and deformity of the T-wave. This evidence, taken in conjunction with our knowledge of the existence of similar disturbances in rheumatic fever, diphtheria, influenza, infarction of the ventricle, and alkaloidal and other poisoning of the myocardium suggests the importance of these deformities of the ventricular electrocardiogram as evidence of injury to ventricular muscle. The injury may be transient, the effect fleeting, and the damage temporary.

SUMMARY

The histopathological examination of the myocardial tissues of animals dead of experimental yellow fever has demonstrated the existence of

well-marked degenerative changes, presenting protean characters, in the musculature of sino-atrial node, auricle, auriculo-ventricular bundle, and ventricle. The impression has not been obtained that the degree of degeneration is greater in one part of the myocardium than in another part; nevertheless, the advantages of considering each part separately from the pathological standpoint are as obvious as those of considering the various portions individually as anatomical and physiological entities. Fatty degeneration of the muscular fibers of the heart, varying in degree and patchy and irregular in distribution, has been a constant finding in experimental yellow fever. Granular degeneration of the myocardium has been of equally common occurrence. In other instances, but in most cases in lesser degrees, hyaline and vacuolar types of muscle degeneration have been encountered. A characteristic but not a constant finding, recalling a similar one observed in diphtheritic hearts, has been a patchy myolysis of isolated muscle-fiber groups. Occasional small petechial hemorrhages have been observed scattered through the myocardium. Only rarely have cellular infiltrations been met with as small numbers of lymphocytes and endothelial leucocytes clustered about the smaller blood vessels. In the rarer instances, when these inflammatory cells have been observed, it is thought that the degenerating tissue has afforded the chemotactic stimulus for their response. The lesions of the myocardium, like those in the parenchymal tissues of other organs, are primarily degenerative in character. The degenerative lesions of the myocardium in yellow fever represent a well-marked structural basis for the occurrence of functional disturbances in its various parts.

The author wishes to express his thanks to Dr. D. A. Irwin, who took the microphotographs here presented, and to Dr. W. A. Sawyer and Dr. S. F. Kitchen who kindly secured many specimens for him. The aid, advice, and generous concession of time and knowledge afforded the writer by Professor Oskar Klotz have been of the greatest assistance in the performance of the work.

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CHANGE IN THE SIZE OF THE HEART IN SEVERE ANEMIA

With Report of a Case

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ENLARGEMENT of the heart and the presence of systolic murmurs, in cases of severe anemia, have been recognized and well known for many years. Most of the observations are based upon clinical and post-mortem findings in cases of pernicious anemia.

The character of the murmurs may differ in no way from those heard in mitral disease of rheumatic or atherosclerotic origin. The severe anemias of rheumatic infection are well recognized. The problem then confronts the clinician as to whether or not the cardiac condition is dependent upon the anemia or is dependent upon true structural changes. If a surgical procedure is contemplated, the problem becomes acute. The following case shows how great this difficulty may be and illustrates how an enlarged heart, with apical and basal murmurs simulating organic valvular disease, may return to normal with relief of the anemia.

After an extensive search of the literature, I have been unable to find a case, proved roentgenologically, of definite enlargement of the heart in severe secondary anemia with a subsequent decrease in size associated with a return of the blood picture to normal. This report is based upon such a case.

CASE REPORT

E. K., a woman, aged 35 years, sought medical aid on February 25, 1930, complaining chiefly of profound weakness and dyspnea on slight exertion. She had been married for twelve years and had three children, the youngest of whom was four years old. Her past history was entirely negative. There was no history of rheumatic fever, chorea, tonsillitis, or joint pains. She was perfectly well until six months before when she began to bleed profusely with her menstrual periods. Menses remained regular and the severe menorrhagia continued each month. She gradually lost strength and about fifteen pounds in weight, and for two to three weeks noticed increasing dyspnea on exertion. One week before she had felt a "lump" in her lower abdomen.

Physical examination revealed a fairly well-nourished adult female with marked pallor of the conjunctivae, lips, and skin. She did not appear acutely ill. The heart was enlarged to both the right and the left on percussion. A loud, blowing, systolic murmur was present all over the precordium, but was heard best in the third and fourth interspaces about an inch to the left of the sternum. No diastolic murmur could be heard. The second pulmonic sound was louder than the second aortic sound. Blood pressure was 140/80 mm. The rest of the physical examination was negative except for a hard, nodular mass rising out of the pelvis and reaching to within 6 cm. of the umbilicus.

Teleroentgenogram (Fig. 1*A*) showed a generalized enlargement of the heart to the left and right and a moderate straightening of the left border with slight bulging in the region of the pulmonary conus, the picture of an advanced mitral lesion. The total transverse diameter of the heart (13.3 cm.) was greater than half of the transverse diameter of the thorax (26.0 cm.).

Electrocardiogram (Fig. 2*A*) showed a normal sinus rhythm with a left ventricular preponderance. On February 28, 1930, the hemoglobin was 35 per cent and the red blood cell count 2,500,000 per cubic millimeter. The white blood cells numbered 9000 per cubic millimeter with 68 per cent polymorphonuclears and 32 per cent lymphocytes. The patient was hospitalized and carefully observed. She

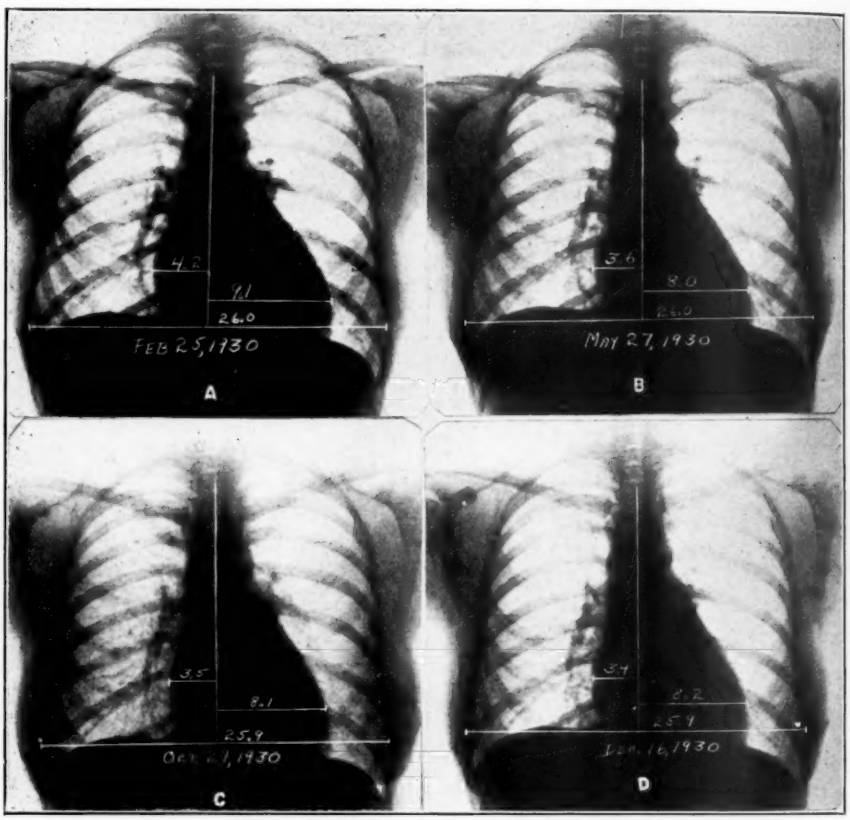

Fig. 1-*A*.—Note enlargement of the heart to right and left with typical "mitral contour." Total transverse diameter of heart 13.3 cm.

Fig. 1-*B*.—Decrease in size of right and left heart. Total transverse diameter of heart 11.6 cm. Decrease of 1.7 cm.

Fig. 1-*C*.—Same size and shape of heart as in Fig. 1-*B*. Total transverse diameter of heart 11.6 cm.

Fig. 1-*D*.—Same as Fig. 1-*C*. Total transverse diameter of heart 11.6 cm.

was menstruating profusely at the time and continued so until March 6, 1930. The temperature remained normal. The hemoglobin was estimated daily and varied between 35 per cent and 41 per cent. The cardiac picture remained unchanged. It was decided that the severe secondary anemia due to bleeding fibroids was probably the cause of the cardiac findings, and that hysterectomy had to be done to remove the cause and to stop the progression of the severe anemia in an attempt to pre-

vent further cardiac damage. On March 8, 1930, the patient was given a direct transfusion of 500 c.c. of blood, and this was followed by a slight rise in temperature. Hemoglobin the next day had risen to 62 per cent and by March 16, 1930, had reached 72 per cent, and the red blood cells numbered 3,900,000 per cubic millimeter. The next day the patient was operated upon by Dr. Robert T. Frank. A large fibromyoma of the uterus was found. A supravaginal hysterectomy, bilateral salpingo-oophorectomy and appendectomy were done. The patient had an uneventful postoperative course. The hemoglobin ranged between 70 and 74 per cent. The patient left the hospital on April 3, 1930. The heart appeared definitely smaller on percussion, and the loud systolic murmur previously heard was barely audible.

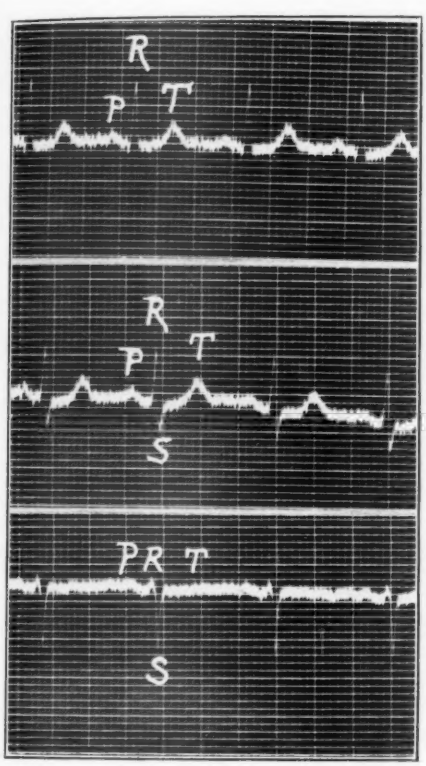

Fig. 2-*A*.

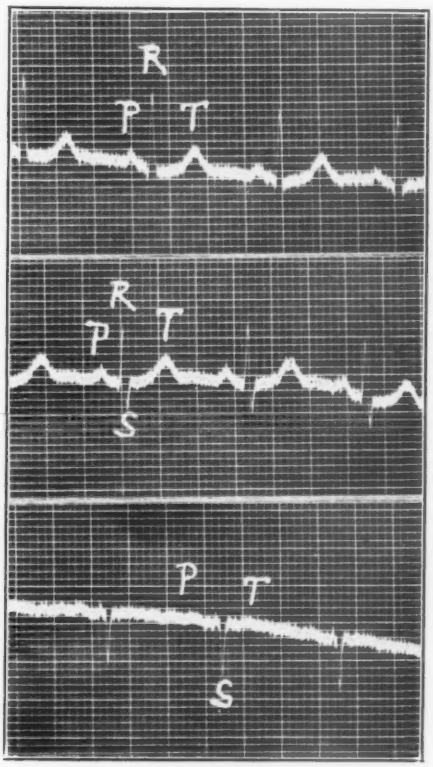

Fig. 2-*B*.

Fig. 2.—*A*, Taken February 25, 1930. Left ventricular preponderance. *B*, Taken December 16, 1930. Left ventricular preponderance, slightly less than *A*.

Teleroentgenogram (Fig. 1*B*) taken on May 27, 1930, three months after the first one, showed a marked decrease in the size of the heart with only slight evidence of "mitralization" of the left border. The total transverse diameter of the heart was 1.7 centimeters less, this diminution involving both the right and left sides of the heart. On examination at this time, the heart sounds were all normal and a faint, soft systolic murmur could be heard at the apex. On held inspiration the murmur disappeared entirely. The patient was symptom free.

A third teleroentgenogram (Fig. 1*C*) taken on October 27, 1930, was the same as the previous one, with practically no evidence of mitralization. The hemoglobin at this time was 95 per cent. Heart sounds were normal, and no murmurs could

be heard even after exercise. The heart at this time, both clinically and radiographically did not reveal any evidence of organic or functional disease.

A fourth teleroentgenogram (Fig. 1*D*) taken on December 16, 1930, was the same as the previous one.

An electrocardiogram taken at this time (Fig. 2*B*) was practically the same as the original one except that the left ventricular preponderance was slightly less marked.

The patient was first seen in consultation. Because of the marked subjective complaints and the cardiac findings, it was felt that the patient probably had an organic valvular defect and that the symptoms were aggravated by the severe anemia. The subsequent course of the case proves rather conclusively that the change in circulatory dynamics was due to the anemia and not to structural changes in the heart.

The earliest observations on the behavior of the heart in anemia deal with cases of "chlorotic" individuals. Irvine[1] in 1877, Barrs[2] in 1891, and Hersman[3] in 1893 described murmurs that disappeared with a cure of the anemia. Gautier[4] in 1899 found cardiac enlargement by percussion in twenty out of twenty-two cases of chlorosis. Kraus[5] in a review of forty-seven cases of pernicious anemia found cardiac dilatation in thirty on percussion. Goldstein and Boas[6] found that cardiac dilatation as well as hypertrophy occurred not only in pernicious anemia, but also in severe secondary anemia. Lewis and Drury[7] state that the heart can dilate because of an insufficient blood supply to it. Lüdke and Schüller[8] produced enlargement of the heart in dogs, experimentally by rendering the animals anemic. Fahr and Rhonzone[9] describe the circulatory dynamics in severe anemia showing how the increased work of the heart produces ventricular hypertrophy.

The above observations and the clinical course seem to support the belief that the case herein reported was probably almost entirely in the nature of dilatation. The total transverse diameter of the heart decreased almost 2 cm. in three months. Clinically this change was observed within one month, obviously too short an interval for hypertrophy to disappear.

SUMMARY

A case of severe anemia due to bleeding fibroids is presented, showing that the dilated heart of anemia may become smaller in size and normal in shape, as proved by teleroentgenograms, very soon after the cause of the anemia is checked and the blood picture returns to normal. Cardiac enlargement is a frequent finding in patients suffering with severe anemias. Roentgenologically, the enlarged heart of anemia often cannot be differentiated from the picture of organic valvular disease. The enlarged heart found in severe anemias may decrease in size when the anemia is cured. The cardiac murmurs heard in severe anemias can disappear entirely when the anemia is

cured. The finding of an enlarged heart together with the typical physical signs and x-ray picture of organic valvular disease in a patient with a severe anemia, does not in itself indicate organic cardiac disease.

I wish to express my appreciation to Dr. Marcus A. Rothschild for his helpful suggestions.

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THE ELECTROCARDIOGRAPHIC CHANGES IN MYOCARDIAL ISCHEMIA*

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I. The Effects of Ligation of the Left Descending Coronary Artery With and Without Occlusion of the Inferior Vena Cava

IN PREVIOUS papers[1, 2] we reported our observations on the electrocardiographic changes in experimental and clinical pericardial effusion. Deformities in the R-T complex similar to those seen in recent myocardial infarction were observed. These changes were ascribed to myocardial ischemia resulting from increased hydrostatic pressure in the pericardial sac. The present work was undertaken to study further the effects of acute experimental myocardial ischemia on the electrocardiogram. For this purpose the ramus descendens of the left coronary artery alone was tied. Further reduction in the blood supply to the heart was induced by occlusion of the vena cava inferior.

Experimental occlusion of the coronary arteries is known to cause changes in the R-T complex.[3, 4, 5, 6, 7] Recently Gruber[8] found that generalized anoxemia caused electrocardiographic changes which were exaggerated by drugs which presumably constrict the coronary arteries.

METHOD

Twenty-nine dogs ranging in weight from fourteen to thirty-eight kilograms were used. The animals were anesthetized with morphine and barbitol. The chest was opened and artificial respiration instituted. The pericardium was split and attached to the chest wall to form a hammock for the heart. In this way a reasonably constant position of the heart was maintained throughout the experiment. Under the inferior vena cava a half-inch tape was placed, which when pulled taut occluded the vessel. The ramus descendens of the coronary artery was freed from its sheath, and a waxed silk thread was placed under it. The vessel was ligated at varying levels (1 to 4.5 cm.) from the mouth of the left coronary artery. In a few preliminary experiments the coronary vein was occluded in the tie. After a variable period following the coronary tie (9 to 58 minutes) the inferior vena cava was temporarily occluded for from 3 to 5 minutes.

Electrocardiograms were taken, using the three standard leads, immediately before (control), at various stages after the coronary tie, and during the occlusion of the inferior vena cava. In most of the experiments a continuous mean blood pressure tracing was recorded. At the end of each experiment the heart was

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injected by Gross's barium sulphate method.[9] This procedure afforded a check on the completeness of the experimental tie and showed the extent of the anastomosis in the area supplied by the occluded vessel.

RESULTS

The principal effects on the electrocardiogram of ligation of the ramus descendens of the left coronary artery may be considered under three headings as follows:

I. The Effect on the Cardiac Mechanism.—Twenty-six successful coronary ligations were made. In eight of these death as a result of ventricular fibrillation occurred within five minutes. Six animals developed ventricular fibrillation within eleven to seventeen minutes; three developed dilatation and fibrillation of the ventricles (seventeen, forty, and forty-six minutes, respectively after the coronary tie) as a result of manipulation. The remainder, nine in number, were sacrificed from thirty-eight to sixty-eight minutes after the coronary tie. In other words, ventricular fibrillation directly attributable to coronary occlusion occurred in approximately 54 per cent of our animals within the first hour.

In one instance a record was obtained at the onset of ventricular fibrillation (Fig. 1). After a few premature ventricular beats, the last one of which is shown in the figure, a run of ventricular tachycardia was inaugurated by a premature ventricular beat and terminated by ventricular fibrillation.

Analysis of our curves showed no relation between the presence of ventricular fibrillation and the level at which the artery was tied, the abundance of anastomosis, or the weight of the dogs. In most instances the animals that developed ventricular fibrillation had premature contractions and paroxysmal tachycardia as well.

Ventricular premature contractions were common sequelae, occurring in sixteen animals. In half the cases the premature contractions arose from several foci. Short and long runs of ventricular paroxysmal tachycardia were also common (occurring in ten animals). In several instances the paroxysmal tachycardia arose from several foci. In one case, the origin was auricular. Sinus bradycardia developed in three animals and sinus tachycardia in two others. In four animals no change of mechanism occurred.

II. The Effect on the Mean Blood Pressure.—Ligature of the coronary artery led to surprisingly small changes in the mean blood pressure. In only six out of nineteen animals in which it was recorded, did the blood pressure drop permanently following the coronary occlusion, and this drop was only from 5 to 20 mm. Hg. In four others there was a temporary drop followed by a return to normal or actually to a level higher than normal (10 mm. Hg. in one and 25 mm. Hg. in the other). In four animals no change in blood pressure occurred. In five the blood pressure rose from 10 to 30 mm. Hg. following the coronary

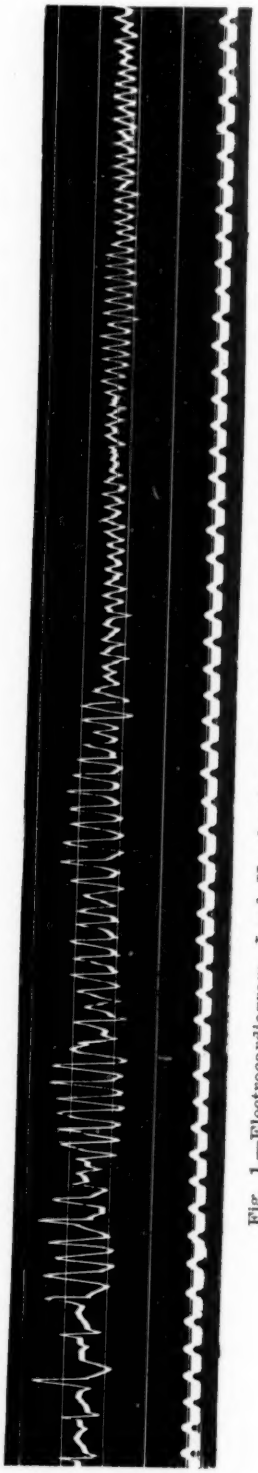

Fig. 1.—Electrocardiogram, Lead II, showing the onset of ventricular fibrillation. Time 0.2 sec.

tie; in one of these, however, the pressure later dropped to below normal. In every instance a decided drop in blood pressure occurred with premature contractions and paroxysmal tachycardia. The magnitude of the drop varied from 20 to 40 mm. of Hg.

III. The Effect on the R-T Segment and the T-wave of the Electrocardiogram.—Occlusion of the left descending coronary artery alone caused only slight alteration in the R-T segment, provided the mechanism remained normal. The only change that did occur in most of the cases was in the T-wave. This consisted in an increase in the amplitude of an upright T (c.f. segments 1, 3, and 7 in Fig. 2), a decrease in the amplitude of an inverted T (c.f. segments 1, 3, 5, 8, in

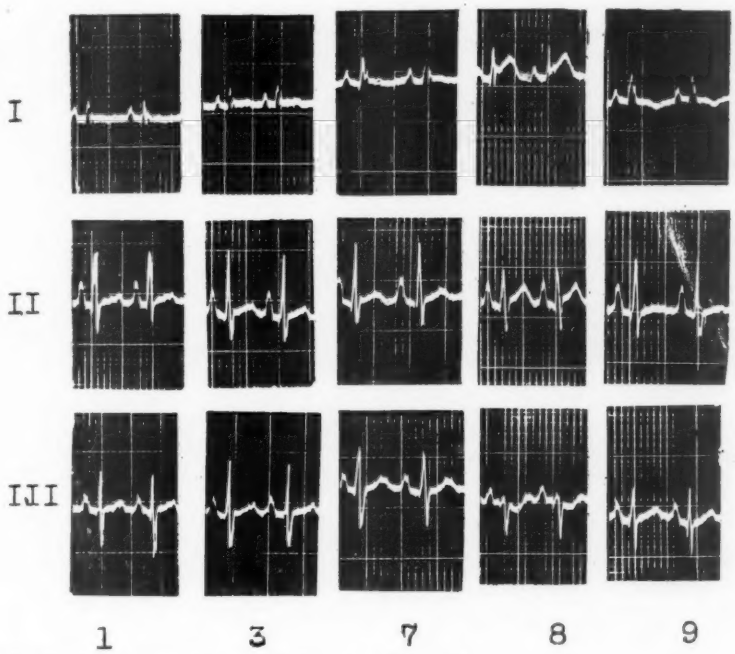

Fig. 2.—Typical segments of experiment on Dog 16.
(1) Control.
(3) Seven minutes after left coronary was tied.
(7) Forty minutes after left coronary was tied.
(8) Forty-five minutes after left coronary was tied and five minutes after inferior vena cava tie.
(9) Fifty minutes after left coronary was tied and five minutes after vena cava tie was released.

Fig. 3), and the transformation of a small inverted T into a small upright one (c.f. segments 1 and 2 in Fig. 5).

In two control animals ligatures were placed under the coronary arteries but not tied. This procedure alone caused slight directional change in the T-wave. It would seem, therefore, that little significance can be attached to the minor changes in the T-wave after coronary ligation.

In two animals in which the vein as well as the artery was tied,

slight characteristic changes in the R-T segment were present with normal mechanism.

The appearance of frequent premature contractions or of paroxysmal tachycardia was followed in practically all cases by characteristic

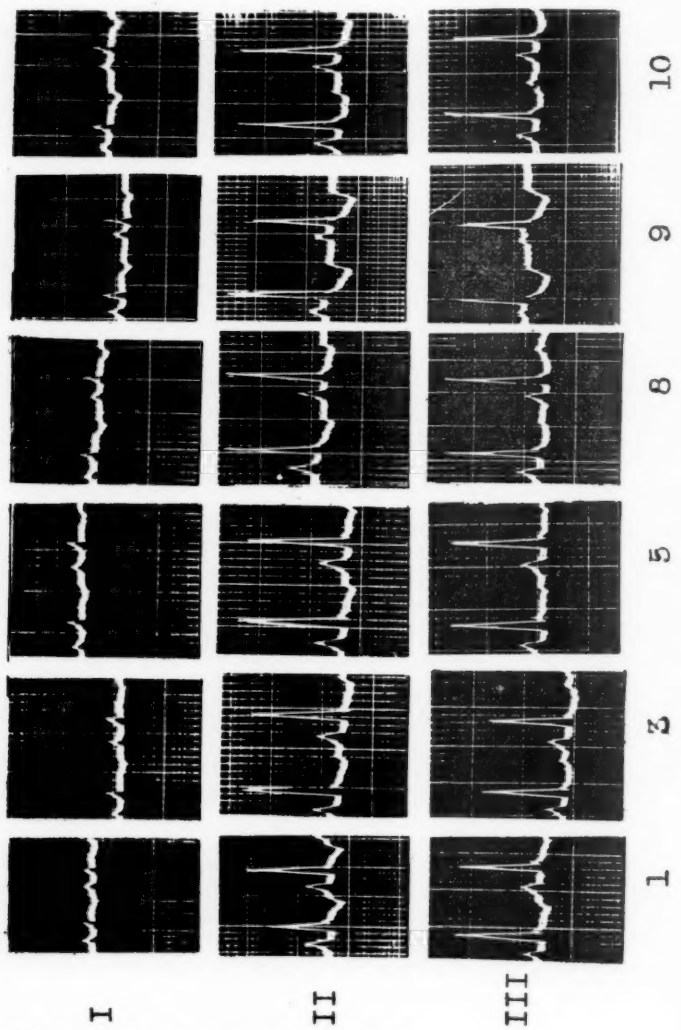

Fig. 3.—Typical segments of experiment on Dog 21.
(1) Control.
(3) Six minutes after left coronary was tied.
(5) Thirty minutes after left coronary was tied.
(8) Forty-two minutes after left coronary was tied.
(9) Forty-seven minutes after left coronary was tied and five minutes after inferior vena cava tie.
(10) Fifty-two minutes after left coronary was tied and five minutes after inferior vena cava tie was released.

R-T deviations which tended to disappear with the restoration of a normal mechanism. This is well shown in Figs. 4, 5 and 6. Dog 26, whose record is shown in Fig. 4, developed frequent premature con-

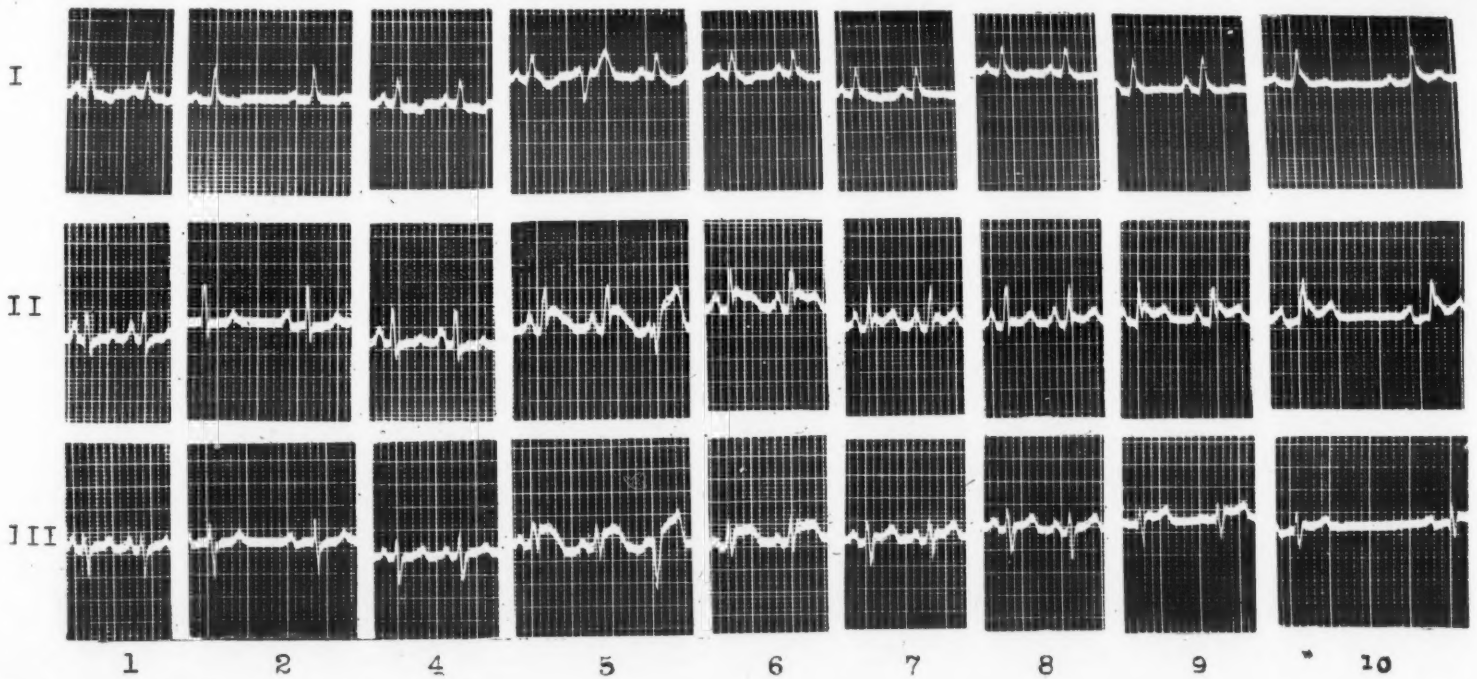

Fig. 4.—Typical segments of experiment on Dog 26.

(1) Control.
(2) Inferior vena cava tied for five minutes.
(4) Sixteen minutes after inferior vena cava tie was released.
(5) Two minutes after left coronary was tied.
(6) Ten minutes after left coronary was tied.
(7) Twenty minutes after left coronary was tied.
(8) Thirty minutes after left coronary was tied.
(9) Thirty-four minutes after left coronary was tied and four minutes after inferior vena cava tie.
(10) Thirty-nine minutes after left coronary was tied and five minutes after inferior vena cava tie was released.

tractions occurring singly and in short runs and coming from several foci. This irregularity started about a minute after the coronary was tied, reached its maximum two minutes later, and disappeared within ten minutes. (See segment 5 of Fig. 4.) The positive S-T segment in Leads II and III is apparent, as is the short positive S-T followed by a negative T in lead I. These abnormalities are in sharp contrast to the normal configurations of the electrocardiogram in segment 4, the control. Segments 6, 7 and 8 of Fig. 4 show the return of the electrocardiogram to normal in a period of thirty minutes. Segment 8 differs from the control segment 4 only in that it has a larger T in Leads

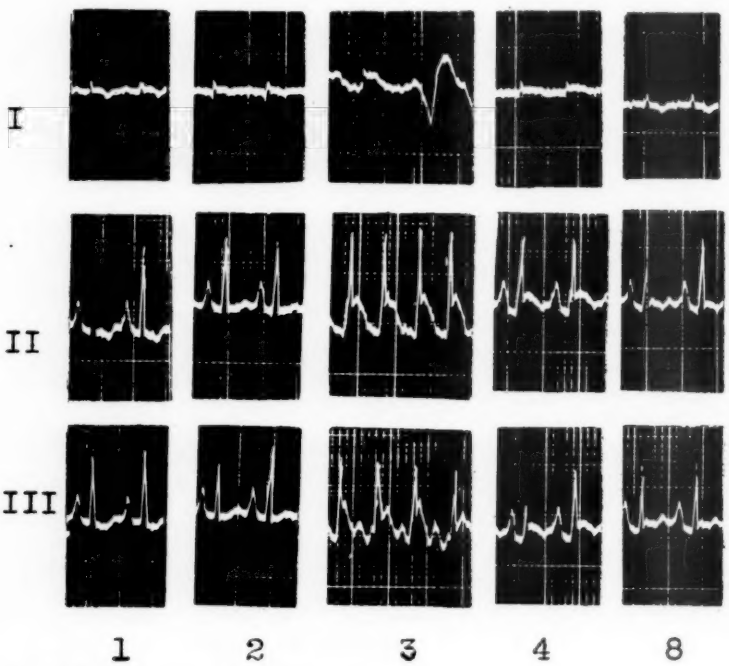

Fig. 5.—Typical segments of experiment on Dog 18.
(1) Control.
(2) Four minutes after left coronary was tied.
(3) One minute after left coronary was tied.
Paroxysmal tachycardia stopped by stimulation of peripheral left vagus.
(4) Two minutes later and eleven minutes after left coronary was tied.
(8) Thirty-nine minutes after left coronary was tied.

II and III with a slight slurring of the descending limb of R in Lead I. Dog eighteen whose record is shown in Fig. 5, developed auricular paroxysmal tachycardia, interrupted by short runs of ventricular tachycardia. This irregularity was interrupted and a normal mechanism restored by stimulating the peripheral end of the left vagus with a faradic current. Except for the T-wave becoming upright, no change occurred in the electrocardiogram four minutes after the coronary ligation (c.f. segments 1 and 2). During the tachycardia, segment 3, a high take-off of the S-T segment is seen. This persists in a milder

form two minutes after the tachycardia was interrupted, segment 4, and has practically disappeared thirty-nine minutes later, segment 8. Dog 30, whose record is shown in Fig. 6, developed ventricular premature contractions from several foci which on occasion occurred in short runs following the ligation of the coronary artery. Segments 5, 6, and 7 show the high take-off of the S-T segment in the normal sinus beats between the premature contractions.

It appears, therefore, that an abnormal cardiac mechanism (premature contractions and tachycardia) is a factor in myocardial ischemia. In hearts developing an abnormal mechanism following coronary ligature, positive R-T deviations occurred. On the other hand, no such changes were seen in hearts which continued to beat normally following coronary ligature. The intervention of a cardiac irregularity in a heart already partially deprived of its blood supply, acts as an added insult by further impairing the coronary flow.

IV. The Effect of Inferior Vena Cava Ligation.—In eleven animals the inferior vena cava was temporarily occluded twenty times at various periods after the coronary ligation (nine to fifty-eight minutes). The occlusion lasted from three to five minutes. In every case the mean blood pressure fell to a level ranging from 45 to 60 mm. Hg., with one exception when it fell to 70 mm. Hg. This represented a drop in pressure ranging from 40 to 80 mm. Hg.

The most common change in mechanism following the ligation of the vena cava was a sinus bradycardia (17 experiments out of 20). In one animal in which the inferior vena cava tie was made three times no change in mechanism occurred. In one experiment complete heart-block developed. The effect of the inferior vena cava tie on premature contractions was variable. The records of one experiment show (Fig. 6) that the premature contractions present before the vena cava tie disappeared following the tie. In one experiment the cava ligation induced ventricular premature contractions, while in two other instances premature contractions persisted after cava ligation.

As a rule characteristic R-T deviations appeared after ligation of the inferior vena cava. For example, in Dog 16, in which ligation of the coronary artery had no effect on the S-T segment (e.g. Fig. 2 segments 1, 3 and 7), occlusion of the inferior vena cava for five minutes produced a positive S-T take-off in Leads I and II and a negative take-off in Lead III. These changes disappeared again five minutes after release of the ligature on the cava. Fig. 3 illustrates a similar result in Dog 21. In this animal no change in the S-T segment occurred following coronary tie, i.e., segments 3, 5 and 8, until the inferior vena cava was ligated for five minutes (segment 9) when a marked negative S-T segment developed in Leads II and III which tended to disappear five minutes after releasing the caval tie (segment 10). In Fig. 4, is shown the gradual return to normal of the

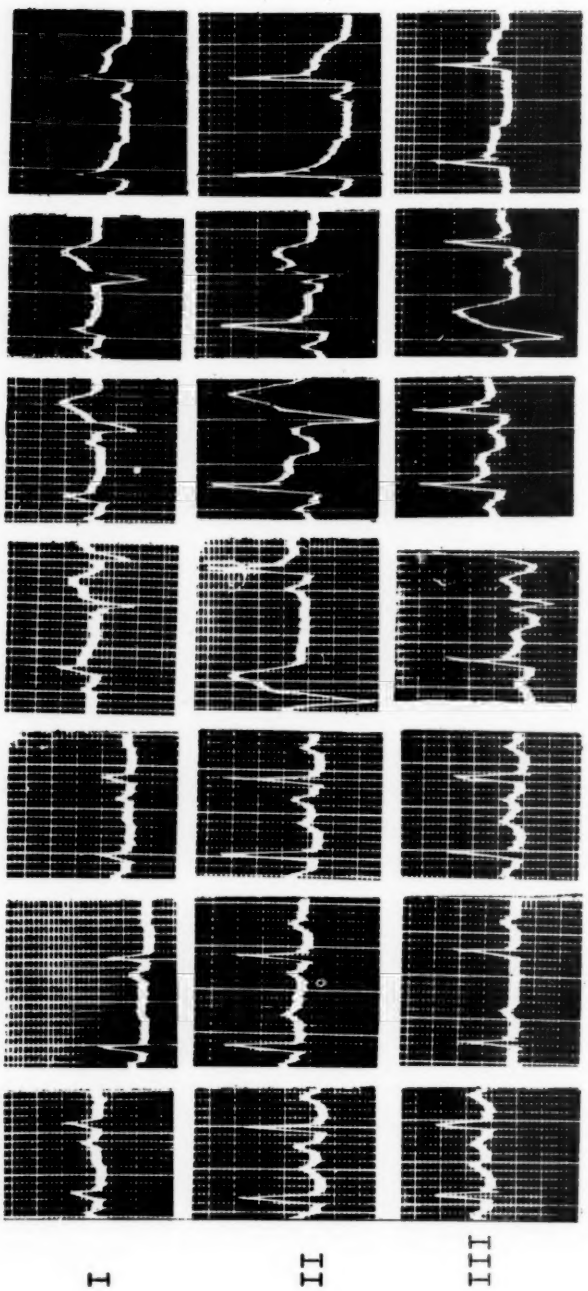

Fig. 6.—Typical segments of experiment on Dog 30.

(1) Control.
(2) Inferior vena cava tied for five minutes.
(4) Twelve minutes after inferior vena cava tie was released.
(5) Two minutes after left coronary was tied.
(6) Five minutes after left coronary was tied.
(7) Eight minutes after left coronary was tied.
(8) Thirteen minutes after left coronary was tied and five minutes after inferior vena cava tie.

S-T deviation following a coronary tie which appears in segment 5 associated with frequent premature contractions (segments 6, 7, 8). After ligature of the inferior vena cava the S-T abnormality reappears (c.f. segments 9 and 10). The effect of occlusion of the inferior vena cava for five minutes in augmenting the S-T abnormality produced by frequent premature contractions is shown in Fig. 6 (c.f. segments 7 and 8). In the majority of instances the S-T deviation caused by ligation of the inferior vena cava tended to disappear when the ligation was released (e.g. segment 9, Fig. 2 and segment 10, Fig. 3).

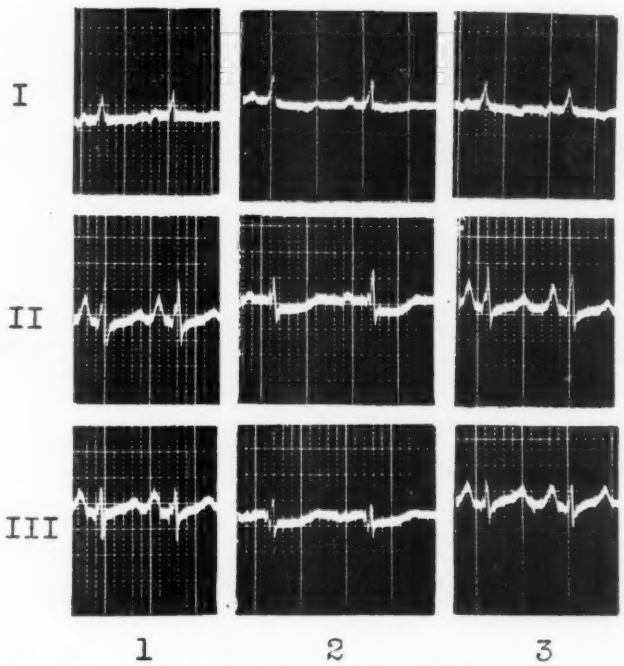

Fig. 7.—Typical segments of control experiment on Dog 31.
(1) Control.
(2) Inferior vena cava tied for five minutes.
(3) Five minutes after inferior vena cava tie was released.

Control experiments were performed. In ten animals the inferior vena cava was tied while the coronary arterial circulation was uninterrupted. Sinus bradycardia occurred in nine of these animals during the cava occlusion. In the other instance sinus tachycardia developed. The mean blood pressure was reduced to a level of 50 to 70 mm. Hg. which indicated a drop from 45 to 90 mm. Hg. The changes in blood pressure in these controls are therefore of the same order as in the other experiments. No changes were present in the S-T segment in most of the controls (e.g. segments 1, 2 and 4 of Fig. 4 and segments 1, 2 and 4 of Fig. 6). In three animals the S-T segment became slightly negative (0.5 to 1 mm. in one or two leads). In

only one animal, Dog 31, whose records are shown in Fig. 7, was a more distinct negative S-T segment observed. Even here the change was in no way comparable to the changes seen in the cava occlusion after ligation of the coronary artery (c.f. Fig. 7 with Fig. 3).*

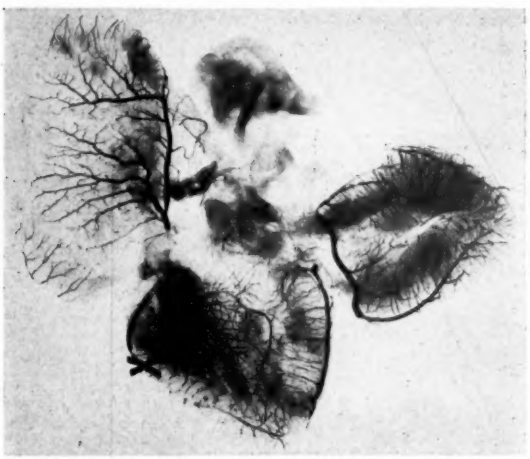

Fig. 8.—X-ray of injected coronary arteries of Dog 16. X indicates location of occlusion of the ramus descendens of the left coronary artery. The three ears in the figure indicate respectively from right to left, the right ventricle, left ventricle, and septum. Note abundance of anastomosis.

Fig. 9.—X-ray of injected coronary arteries of Dog 30. Showing occlusion of ramus descendens of the left coronary artery. The three ears in the figure as in previous figure. Note almost complete absence of anastomosis.

DISCUSSION

(a) *Relation of the electrocardiographic changes to the level of ligation, to the area supplied by the ligated vessel, and to the abundance of the coronary anastomosis.*

*No change in the S-T interval was observed during slowing following stimulation of the vagus.

In these experiments there is no correlation between the extent of the S-T deviation and the animal's weight, the extent of the area deprived of blood supply, or the level at which the ramus descendens was ligated. Especial attention was paid to the extent of the anastomosis, which was found to vary greatly in different animals, from practically none, as illustrated in Fig. 8, to an abundant one as seen in Fig. 9 (c.f. also Moore[10]). Despite this great variation in the abundance of the anastomosis there was no correlation between the anastomosis and the electrocardiographic changes. It may be that this lack of relation is dependent on a variable Thebesian supply, a factor which could not be evaluated.

The lack of R-T deviation associated with normal mechanism in these experiments was not caused by failure of coronary artery ligation. This was shown by the injection of the hearts post-mortem. Every animal showing no changes in the R-T segment after coronary ligation was found on injection to have had complete obstruction of the coronary artery at the site of the tie (e.g. Figs. 8 and 9).

In the face of our negative results from ligature of the coronary artery, we may consider the positive results previously reported. In the first place earlier workers included the vein in the coronary ligature, a factor which must accentuate the ischemia from coronary occlusion alone. In previous experiments, no particular precautions were taken in the use of anesthetics to maintain the systemic blood pressure at a normal level. We found in animals whose left ramus descendens was ligated—with no significant drop in blood pressure—that a lowering of systemic blood pressure from occlusion of the inferior vena cava for five minutes was sufficient to cause R-T deviations to appear. It is apparent, therefore, that unless the systemic blood pressure is maintained at a normal level one cannot conclude that coronary occlusion per se is the sole factor responsible for R-T deviations.

(b) *The Direction of the S-T Deviation.*

Recently Barnes and Whitten[11] have emphasized that the direction of the S-T deviation in the various leads may be used in localizing the site of the area infarcted. According to them infarction of the anterior portion of the left ventricle or apex caused a positive S-T in Lead I and a negative S-T in Lead III, and infarction of the posterior wall of the left ventricle produced a negative S-T in Lead I and a positive S-T in Lead III. Our experiments show that while this correlation obtains in the majority of dogs, it is not always present. The area in which the blood supply was interfered with was located, to a variable extent, in the anterior and apical regions of the left ventricle and in the septum. In 18 experiments a change in the level of the S-T interval occurred in Lead I; in 15 of these the S-T was positive and, in 3, negative. This is in fair agreement with Barnes' and Whitten's pre-

diction. But in Leads II and III the disparity is more striking. For example, in the 25 experiments in which a change in the S-T level occurred in Lead II, in twelve the S-T became positive and in thirteen negative. In the twenty-six experiments in which the S-T level changed in Lead III, ten had a positive S-T, and the remainder (16) a negative S-T. However, the most striking shifts of the S-T level were found in those instances in which the S-T in all three leads or at least in Leads II and III became positive. Some of the typical shifts of the S-T intervals are shown in Figs. 2, 3, 4, 5, 6. For example, Fig. 2 (segment 8) has a positive S-T interval in Leads I and II, and a negative S-T in Lead III. Fig. 3 (segment 9) has practically no change in Lead I and a negative S-T in Leads II and III. Fig. 4 (segment 5) has a short negative S-T in Lead I, and a marked positive S-T in Leads II and III. Figs. 5 and 6 show positive S-T intervals in all three leads.

This variability in S-T changes in hearts with the same general area affected indicates the difficulty of localizing the affected region from the direction of the S-T in the electrocardiogram.

(c) *The Rôle of Myocardial Incompetence in Producing the Electrocardiographic Changes Associated with Coronary Occlusion.*

It was stated above that ligature of the ramus descendens of the left coronary artery in the dog caused no characteristic R-T deformities of the electrocardiogram, provided the cardiac mechanism remained normal, whereas a further impairment in blood supply (ligature of the inferior vena cava for five minutes) caused R-T deviations to appear. In the normally beating dog heart there is apparently sufficient collateral circulation to prevent a high degree of local ischemia following coronary ligature. This collateral supply, however, fails to prevent ischemia after ligature of the inferior vena cava.

The hypodynamic state of the heart resulting from an impaired venous return causes (1) a lowering of intraventricular pressure during systole and (2) a sharp fall in systemic blood pressure, factors which reduce the flow through both the Thebesian system and the coronary capillaries. As a result, myocardial ischemia of a degree sufficient to cause R-T deviations in the electrocardiogram appears. It is known that some grade of myocardial incompetence is often associated with or results from coronary thrombosis in man, and our experimental results suggest that the R-T deviations frequently seen in such cases may be due, in part at least, to the hypodynamic state of the heart.

SUMMARY

Ligature of the ramus descendens of the left coronary artery in acute experiments on dogs caused no characteristic R-T deviations of the electrocardiogram provided the cardiac mechanism remained normal. However, a further impairment in the heart's blood supply induced by ligation of the inferior vena cava for five minutes, produced

typical R-T deviations as seen in recent clinical coronary thrombosis, with a return to normal after the venous obstruction was removed.

The appearance of a disturbance in the cardiac mechanism (extrasystoles and tachycardias) following coronary ligation alone produced R-T deviations.

These experiments suggest that R-T deviation is a manifestation of myocardial ischemia in the production of which coronary occlusion is one factor.

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THE VALUE OF NEEDLE ELECTRODES IN ELECTROCARDIOGRAPHIC DIAGNOSIS*

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IT NOT infrequently happens that, in taking electrocardiograms with the conventional Einthoven leads, using zinc plate electrodes, the auricular deflections are so obscured (by muscle tremor, low voltage, etc.) that it is impossible to decide upon the true character of auricular activity. This is particularly the case with auricular fibrillation,

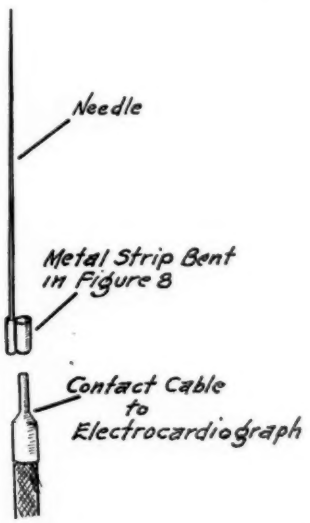

Fig. 1.—Diagram of needle electrodes.

flutter and tachycardia. When such a difficulty occurs, leads from the thorax, with the needle electrodes first suggested by Straub,[1] result in such amplification of the auricular deflections that their true significance can usually be discovered and their rate counted.

Straub found that the site of greatest resistance in the whole system of conduction of heart action currents is the fat-saturated outer layer of the skin. This resistance he could overcome by inserting needles 1 to 2 mm. below the skin surface. Though the needle electrodes were polarizable, he concluded that, since the action current of the heart was small, they would produce no distortion of the electrocardiogram.

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Ackermann[2] compared leads (with needle electrodes) from various points on the thorax with zinc plate leads from the extremities and found that the former showed all the deflections of the normal electrocardiogram with a distinctness often absent from the Einthoven leads.

Wenckebach[3] employed thoracic needle leads in the analysis of cases of auricular fibrillation and flutter and concluded that they were of great value.

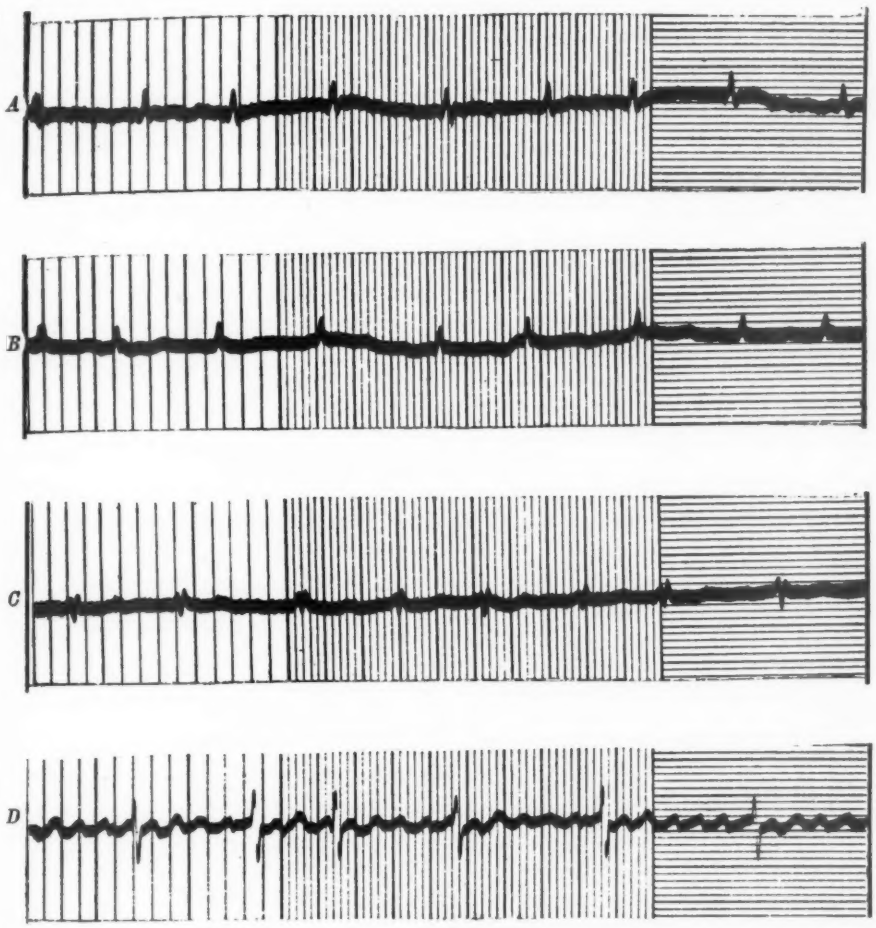

Fig. 2.—Patient 1. *A*, *B*, *C*, the three conventional leads of Einthoven. *D*, A record taken with needle leads from the chest. The irregular auricular rate, indeterminate from records *A*, *B*, *C*, is seen in record *D* to be approximately 470 per minute.

Note.—In all figures the standardization was the same for both needle and ordinary leads, viz., 1 millivolt gave a deflection of 1 cm.

This paper deals with three interesting examples in which our doubts as to diagnosis have been clarified by needle lead records.

The Victor electrocardiograph was used in the cases reported here.*

*Unfortunately we were unable to make an extensive study of needle electrodes with string galvanometers. However, using the Hindle instrument in several cases equally good results were obtained.

The needle leads were of simple construction, consisting merely of an ordinary steel sewing needle connected with the tapered metal ends of the cable from the electrocardiograph (after removing the zinc plates) by a strip of metal bent into a figure eight and tightly clamped around both (Fig. 1). After sterilization the needles were inserted at the second and fifth right interspaces at the sternal margin.

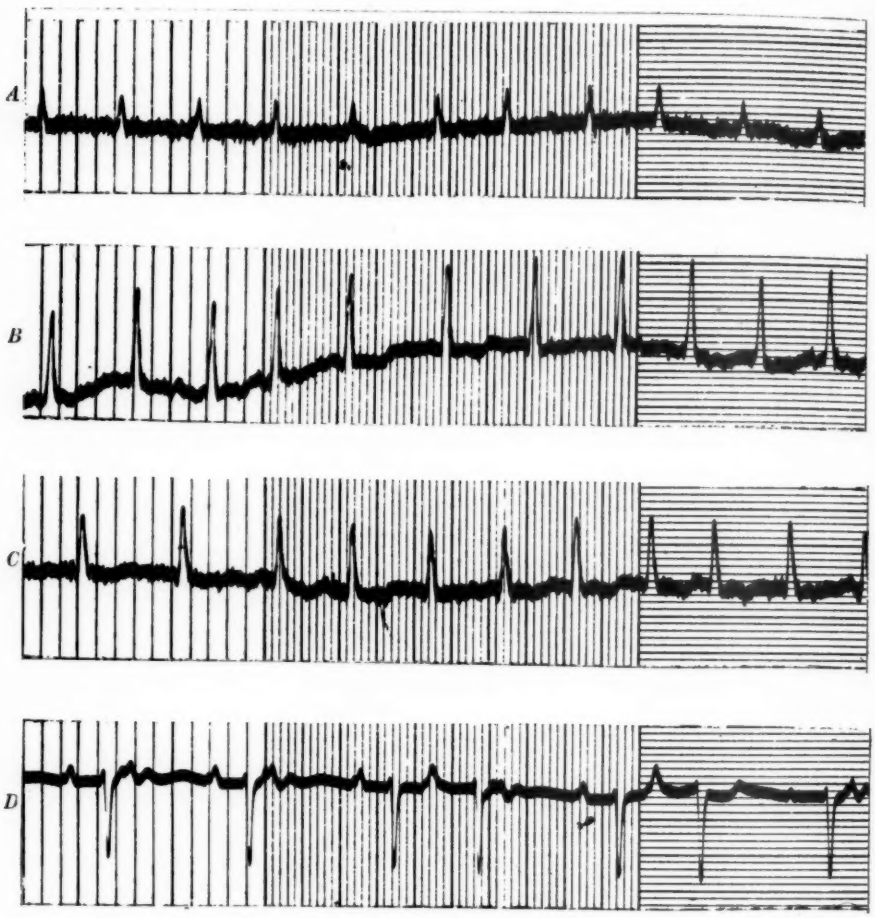

Fig. 3.—Patient 2. *A*, *B*, *C* represent Leads I, II and III. *D* is a needle lead. The skeletal tremor confusing the record from the extremities is eliminated, and the provisional impression of auricular fibrillation is shown to be erroneous, as the P-waves are clearly inscribed, when not buried in the T-waves. The true diagnosis is partial auriculoventricular block with some auricular premature beats.

It must be noted that, in employing needle leads, one can only make use of those connections with the galvanometer marked to lead from the right arm and the left leg, and that the former must always be connected with the needle inserted in the skin in the second right interspace.

In the following cases the true nature of certain auricular arrhyth-

mias was doubtful, until records were obtained with needle leads. Indeed, in Case 2, diagnosis was made possible only by their use.

CASE REPORTS

CASE 1 (Fig. 2). The patient, a colored male, aged 54 years, was admitted to the Cincinnati General Hospital with the clinical diagnosis of arteriosclerotic heart disease, congestive failure and frequent premature contractions. The electro-

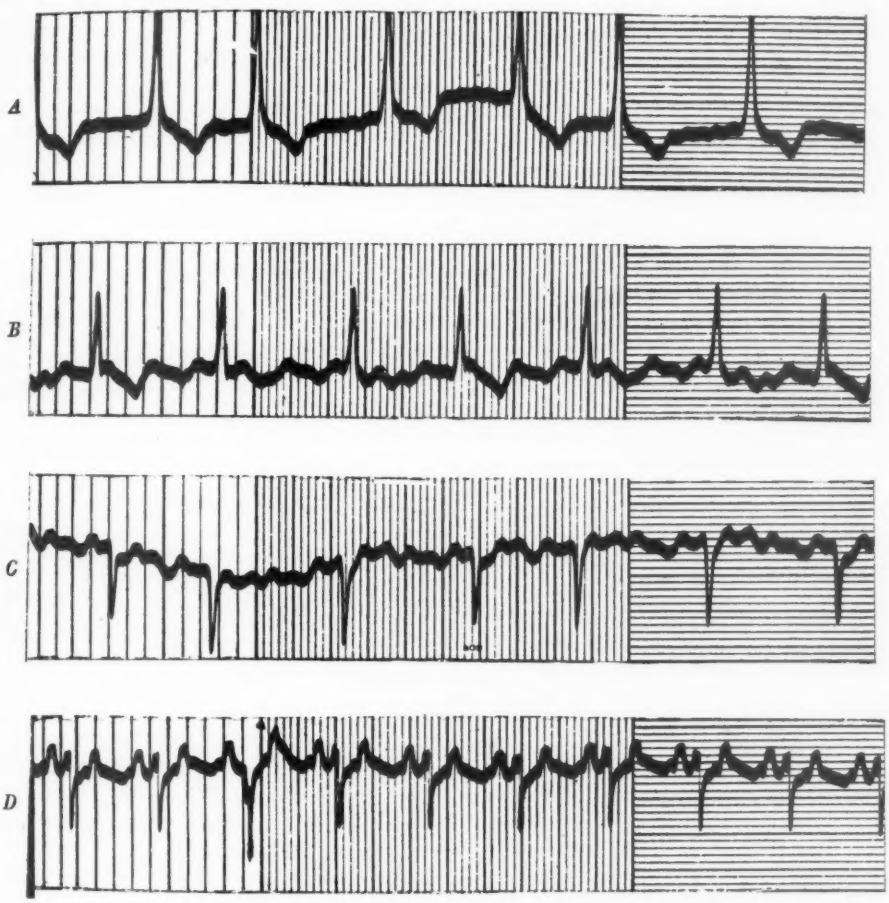

Fig. 4.—Patient 3. Curves *A*, *B*, *C* the standard leads. *D* is a needle lead. This case, originally thought to be possibly auricular fibrillation, is shown to have a completely regular succession of P-waves with a rate of 250 per minute.

cardiogram, with leads from the extremities, showed a rather irregular rhythm, with low voltage. No "f" waves were discernible. The record suggested auricular fibrillation, but auriculoventricular rhythm (type 2) could not be decisively eliminated. A needle lead record showed definite "f" waves, irregularly spaced, with a rate of approximately 470 per minute.

CASE 2 (Fig. 3). This patient, a white female, aged 65 years, was of special interest, as the clinical picture and the electrocardiogram from the extremities suggested auricular fibrillation. However, the needle lead record (Fig. 2 *D*), showed clearly that the arrhythmia was due to partial auriculo-ventricular block with auricular premature beats. Complete auriculo-ventricular dissociation was ruled out, for the P-waves were irregularly spaced.

CASE 3 (Fig. 4). The patient, a colored female of 41 years, was admitted with hypertensive heart disease, mild congestive failure and marked cardiac irregularity. *A*, *B* and *C* of Fig. 3 show Leads I, II and III respectively. These records were at first interpreted as due to auricular fibrillation. But careful measurement suggested a regular spacing of the P-waves, especially in Lead III, though many were buried in the ventricular complexes. The needle lead record, Fig. 4 *D*, showed complete regularity of the auricular waves with a rate of 250 per minute. Consequently, the condition was diagnosed as one of auricular flutter, with varying degrees of block, although the disorder might be paroxysmal auricular tachycardia simulating that of a case reported by White.[4] Later tracings taken after digitalization (and therefore in the presence of a high degree of block), while showing the same auricular rate, resemble more closely those of auricular flutter. It should be mentioned that before digitalis was given, pressure over the vagi and ocular pressure had no effect upon the heart rate.

CASE 4 (Fig. 5) illustrates the extent to which the P-waves can be amplified by the use of needle electrodes.

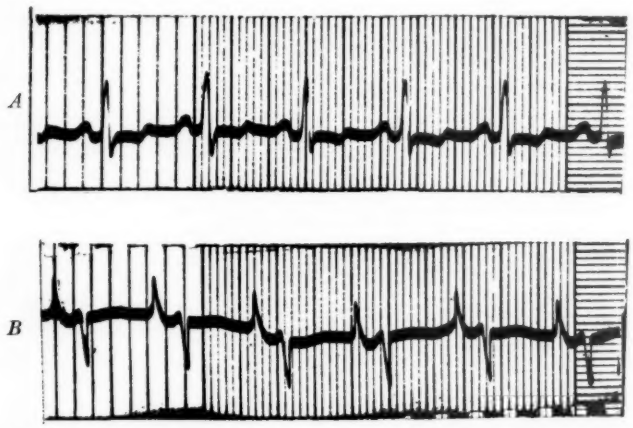

Fig. 5.—Patient 4. *A* is a section from Lead II with ordinary electrodes. *B* is a needle lead from the chest. The P-waves are enlarged disproportionately to the ventricular complexes, which are now registered as downward deflections and show the amplification and change in form of the normal P-wave, which usually occurs in needle leads.

SUMMARY

By the use of needle electrodes and thoracic leads, accurate diagnosis can sometimes be made when the interpretation of electrocardiograms made with the ordinary leads is doubtful. Three cases are cited which demonstrate the value of this method. A simple method for the construction of such electrodes is described.

The authors wish to express their appreciation of Dr. Paul D. White's helpful criticisms and suggestions.

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ELECTROCARDIOGRAPHIC STUDIES IN INFECTIOUS DISEASES*

Preliminary Report

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THE heart is involved in the severer types of all the infectious diseases. The bedside symptoms of this involvement, systolic murmurs, indistinct heart sounds, rapid heart rate, generalized weakness, etc., have been recognized by physicians for many years. An arrhythmia has always been considered of great importance in the establishment of such cardiac involvement. Since the introduction of the electrocardiograph into the clinic, gross abnormalities in electrocardiographic curves have been found in the severer types of nearly all the infectious diseases, typhoid fever, influenza, diphtheria, etc. Auricular fibrillation, flutter, paroxysmal tachycardias, nodal rhythm, extrasystoles, sino-auricular block and all the degrees of atrio-ventricular block have been reported.

In rheumatic fever, more than in any of the other infectious diseases, the arrhythmias have played an extremely important part, primarily because of their frequent occurrence. In recent years many observations have been made, not only on the frequency of changes in rate and rhythm, but also on the high incidence of prolongation of the auriculo-ventricular conduction time. (Parkinson, Gosse and Gennison, Cohn and Swift,[1] and others.) More recently, Cohn and Swift,[2] Rothschild, Libman and Sachs,[3] and others, have made observations on the frequent occurrence of deviations from normal in the ventricular portion of the electrocardiogram. They described changes in the T-wave and in the R-T or S-T intervals as well as conduction disturbances. Swift[4] reported such changes in 93 per cent of a series of rheumatic fever patients. All these observers have reported changes in the form of the electrocardiogram from time to time during the course of the disease, changes not always paralleling the clinical signs of severity, i.e., leucocytosis, temperature, joint involvement, etc.

Rothschild, Libman and Sachs[3] commented upon the persistence of electrocardiographic findings in a number of their rheumatic fever patients who had been declared clinically well. Shapiro,[5] in a recent publication, studied electrocardiographic tracings taken on children who gave a definite history of having had rheumatic fever and who

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were attending school regularly. He found in these children a high percentage of abnormalities occurring particularly in the ventricular portion of the electrocardiogram. In twenty cases of his series he found variations in the form of the electrocardiographic abnormalities from time to time, similar to variations found in active rheumatic fever but to a lesser degree.

The electrocardiographic abnormalities found in rheumatic fever can be thus classified: (1) changes in rate and rhythm; (2) changes in the A-V conduction time, from a slight prolongation of that interval to all the higher degrees of A-V block (3) changes in the ventricular portion of the electrocardiogram involving abnormalities in position and shape of the S-T or R-T interval; height and direction of the T-wave; and height and shape of the main deflection. These changes in themselves cannot be considered specific for any definite disease entity. They have been observed in toxic, degenerative, infectious, vascular, metabolic and other types of disease. We believe that electrocardiographic abnormalities, since they are indicative of a disturbed physiology only, cannot in themselves, without clinical data, be used to make a diagnosis of a specific pathological process. Certain diseases seem to have a predilection for the conduction system, however.

Despite our belief in the nonspecificity of electrocardiographic findings, we felt that in rheumatic fever the above described changes might be characteristic for that disease because of: (1) the high incidence of their occurrence; (2) the varying electrocardiographic changes in the course of the disease, changes not always paralleling the clinical signs or severity of involvement; (3) the tendency of these changes to persist; (4) the frequency of conduction disturbances.

Rothschild, Sacks and Libman[3] compared electrocardiographic findings in rheumatic fever and subacute infective endocarditis. They found these abnormalities much less frequently in subacute infective endocarditis than in rheumatic fever. No mention, however, was made of the possibility of these findings being due to the previous rheumatic involvement that the patients with subacute bacterial endocarditis might have had.

In order to obtain further light on this question, we decided to make comparative studies in other infectious diseases.

We took electrocardiographic curves during the course of the various infectious diseases and compared these findings with those described in rheumatic fever.

Although considerable work has already been done on normal children, we thought it advisable to control our studies in infectious disease with normal children living in the same environment.

In this preliminary report we present briefly the results of a study of two hundred and fifty-nine normal children between the ages of six and fourteen years; fifty cases of scarlet fever, between the ages of

six and fourteen years and fifty cases of diphtheria in the same age groups, and a comparison of the findings in the latter two diseases with those described in rheumatic fever.

RESULTS

I. *Normal Children.*—On the whole our findings do not, in any great degree, vary from the conclusions drawn by Seham,[6] Lincoln and Nicolson[7] and others.

The heart rate decreases as the child grows older, and the female rate is higher than the average male rate. The percentage of cases having a pulse rate above 100 does not strikingly decrease with the increase in age up to nine years; from that age on there is a definite decrease in the percentage occurrence of rates above 100.

Seventy-eight per cent of our normal children have shown a sinus arrhythmia. From the ages of six to nine years there seemed to be a definite decrease in the incidence of sinus arrhythmia with a definite increase in rate; from nine to eleven years, despite a very definite decrease in rate, there was a definite decrease in the incidence of sinus arrhythmia; from the ages of eleven to thirteen years, the incidence of sinus arrhythmia increased very perceptibly, concomitantly with a definite decrease in rate. Extrasystoles were found in only two children—one child had auricular extrasystoles and the other had ventricular extrasystoles. No other arrhythmias were noted.

No abnormalities in the shape of the P-wave were seen in the first or second leads. In 17.6 per cent of this series split, diphasic or inverted P-waves were observed in the third lead.

The average P-R interval in children is much shorter than the accepted maximum normal of 0.20 seconds for adults. Our average for children in the age group studied was about 0.12 seconds, and the range was from 0.08 seconds to 0.16 seconds.

The QRS interval in our series was found to be not more than 0.051 seconds. No abnormalities in the shape of the R-wave or QRS deflections were noted in Leads I or II. In 34.8 per cent of the children there is a slight slurring of the main deflection and a slight widening of the QRS interval seen in the third lead.

We found the R-T or S-T interval isoelectric in the first and second leads in all but four children, and in these four children the distance above or below the line was less than 0.10 mm. No explanation for this possible deviation from the normal could be found in the clinical history.

The average height of the T-wave for the whole series was 3.5 millimeters. No abnormalities of this wave were seen in the first or second leads. Twenty-four and eight-tenths per cent of the children showed an inversion of this wave in the third lead. From the ages of ten to fourteen years there was a very definite decrease in the percentage incidence of inversion of T_3.

The relationship of the length of the P-T to the length of the whole cardiac cycle was studied. It was found that the average P-T interval in these normal children was 71 per cent of the average length of the whole cycle.

In nine children, or 3.4 per cent of our normal series, we noticed an abnormal axis deviation which has persisted for at least two and a half years in four out of five children reexamined within that time.

In twenty-five children studied before and immediately after a given amount of exercise, we found no change in the configuration of the electrocardiographic curve. There were no disturbances in the shape and position of the T-wave or shape and position of the R-T or S-T interval in the first and second leads. No changes in the length of the P-R interval were noted. The only changes noted after exercise were an increase in heart rate and a decrease in the occurrence of sinus arrhythmia.

Daily electrocardiograms were taken on twenty children for two weeks. No changes in the form of the electrocardiogram, either in the T-wave or R-T or S-T interval were noted from day to day in the first and second leads. Changes in the direction of the T-wave in the third lead, however, were observed in three children of this series. Rate changes were frequent. Particular attention was paid to T-wave, R-T and P-R interval changes.

II. *Scarlet Fever.*—There are many relationships that scarlet fever and rheumatic fever seem to have in common. The association of some form of streptococcus to these diseases as a specific etiological factor; the many symptoms of a hypersensitive state caused by some form of this type of organism; the not infrequent activation of a latent rheumatic fever by the occurrence of scarlet fever; the many controversial points in the pathology of these diseases, particularly the conception of Schmorl and Fahr; the many clinical manifestations, tonsillar involvement, joint manifestations, cardiac complications, nephritis, common to both diseases make this comparative electrocardiographic study of interest.

Electrocardiograms were taken during the course of the disease in fifty children suffering from scarlet fever.

We found that the rate did not materially differ in the various age groups from the rate found in normal children. The higher rates, found in the febrile cases, had a definite relationship to the increase in temperature.

The incidence of sinus arrhythmia paralleled the incidence of that arrhythmia in normal children.

A relative bradycardia was observed in 25 per cent of the patients. This marked drop in heart rate was first noted about the tenth day of the disease, and lasted up to about the end of the third or the beginning of the fourth week. No other arrhythmias were noted.

We observed an abnormal axis deviation in 16 per cent of the cases. This deviation, however, returned to normal before discharge from the hospital in all but one child.

No abnormalities in the P-waves were noted. The P-waves, however, were slightly higher in those children having fever than those in the afebrile stage. The average height of this wave in all cases of scarlet fever was 1.9 millivolts as compared with 1.7 millivolts in normal children.

The P-R interval ranged from 0.08 seconds to 0.18 seconds. The average length of this interval was 0.125 seconds. The febrile cases seemed to have a shorter P-R interval. No prolongations of this interval were noted.

No abnormalities or abnormal prolongations of the QRS interval, or of the shape of the main deflection, were noted in the first or second lead.

In 14 per cent of the children minor changes in the position of the R-T or S-T interval were noted in the first or second lead.

Abnormalities in shape and direction of the T-wave in Leads I and II were noted in only 10 per cent of the children. All abnormalities appeared early in the course of the disease and disappeared early in convalescence. No electrocardiographic abnormalities were noted on discharge from the hospital. In 40 per cent of these children an inversion of the T-wave in the third lead was noticed some time during the course of the disease. In 36 per cent T_3 changes only were found. These changes were not considered evidence of myocardial disease although the percentage of inversion of T_3 was higher in scarlet fever than in normal children of the same age groups.

The ratio of P-T to P-P was 70.8 per cent.

Our electrocardiographic findings in scarlet fever differ from those described in rheumatic fever: (1) in the comparative infrequency of abnormalities of the ventricular portion of the electrocardiogram; (2) in the complete clearing up of these abnormalities early in the convalescence; and (3) in the absence of conduction disturbances.

III. *Diphtheria.*—This electrocardiographic study in diphtheria was prompted both by the disturbances found in the ventricular portion of the electrocardiogram in rheumatic fever and also by the endeavor to throw further light on the cause of circulatory failure in that disease.

Fifty consecutive admissions to the diphtheria wards of the Kingston Avenue Hospital for Contagious Diseases were studied. Our series included tonsillar, septic, pharyngeal, laryngeal, and faucial diphtheria. Only mild cases were seen. All children recovered.

In the diphtheria cases the average heart rate was somewhat higher than that found in the scarlet fever or normal children. There was a decidedly higher percentage of cases with rates between 110 and 120 in this disease. This increase in rate was not accounted for by fever.

Fifty-six per cent of the patients showed a sinus arrhythmia. Two cases only showed a relative bradycardia during the second week of the illness. Auricular extrasystoles were noted in only one case.

No abnormalities in either the height or the shape of the P-wave were noted in the first or second leads. P_3 changes alone were not considered evidence of myocardial disease.

No prolongation of the auriculo-ventricular conduction time above that considered normal for children was observed. The average P-R interval, however, 0.134 seconds, was slightly higher than that for scarlet fever.

In order to compare the P-R interval in scarlet fever and diphtheria with that in rheumatic fever, the P-R interval in fifty children, between the ages of six and fourteen years, having acute or subacute rheumatic fever was measured. It was found that the mean and standard deviation of the P-R interval in scarlet fever were respectively 0.1256 and 0.0208; in diphtheria 0.1274 and 0.0202; and for rheumatic fever 0.1936 and 0.034. No prolongations of the P-R interval above that considered normal for children were observed.

The average length of the QRS interval in diphtheria was 0.06 seconds. This is somewhat higher than the average for normal children and for children suffering from scarlet fever. In 16 per cent a distinct widening of this period was noted. In these cases a slurring of the descending limb of the R-wave and a high position of the R-T interval was noted. Aberrations in the QRS group in the third lead only were not considered evidence of myocardial disease; they occurred in 40 per cent of the children. This percentage is slightly higher than that found in normal children and in scarlet fever.

Sixty per cent of the children showed disturbances in the shape or position of the R-T or S-T interval. In 16 per cent the R-T interval was a continuation of a slurred descending limb of the R-wave and did not reach the base line; it had its convexity downward and ended as the upstroke of the T-wave. The QRS interval in these children was widened. By far the greatest number of electrocardiographic abnormalities in mild diphtheria were found in disturbances of the R-T or S-T interval. These abnormalities occurred as early as the fourth day of the disease and as late as the fifty-seventh day. In 14 per cent these abnormalities disappeared entirely before discharge from the hospital. In some instances these curves became normal as early as the seventh day and in others not before the sixty-third day of the disease. In 46 per cent of the cases these abnormalities persisted up to the time of discharge from the hospital to some degree. There seemed to be, however, a tendency to improvement.

No relationship was noted between the occurrence of these abnormalities and temperature, heart rate or duration of illness.

Of these children only eleven showed clinical signs of myocardial involvement during the course of the disease.

Abnormalities in the T-wave were noted in eighteen children. Diphasic, iso-electric, depressed or rounded T-waves were considered abnormal. No inversions of this wave in the first or second leads were noted, however. T-wave changes, as well as the R-T interval changes, occurred as early as the fourth day of the disease and as late as the fifty-seventh day.

The ratio between P-T and P-P did not differ to any degree from that of normal children or of children with scarlet fever. It was 71 per cent of the whole heart cycle.

Eighteen per cent of the children showed an abnormal axis deviation; 12 per cent showed a right axis deviation and 6 per cent a left axis deviation. Of the nine children who showed an abnormal axis deviation, seven showed electrocardiographic abnormalities and six showed clinical evidence of myocardial involvement. In only one of these children was the heart found large by roentgen-ray examination.

It seems to us that these electrocardiographic evidences of myocardial disturbances in mild diphtheria without any prolongations of the P-R interval is evidence to support the myocardial theory in circulatory failure in this disease.

We feel that electrocardiographic abnormalities may be the only evidence of myocardial involvement, and that children suffering from diphtheria should not be pronounced free from danger without the benefit of further electrocardiographic studies.

These electrocardiographic abnormalities in diphtheria are similar to those described in rheumatic fever: (1) in that they occur in a high percentage of children who suffer from only very mild diphtheria; (2) that these findings have a tendency to persist; and (3) that electrocardiographic abnormalities may be found when no clinical signs of myocardial involvement are present.

They differ, however, in the absence of A-V conduction disturbances in these milder cases.

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INHALATIONAL TREATMENT OF ANGINA PECTORIS AND INTERMITTENT CLAUDICATION*

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INHALATION of carbon oxide is now administered for various therapeutic and prophylactic purposes. The benefits afforded depend chiefly on the part which carbon dioxide plays in the control of respiration. Resuscitation from asphyxia of the newborn,[1] prevention of postoperative atelectasis and pneumonia,[2] elimination of ethyl ether,[3] of carbon monoxide,[4] and of other anesthetic and toxic gases[5] from the lungs and blood, all alike depend upon the increase of pulmonary ventilation under stimulation of the respiratory center by inhalation of carbon dioxide.

INFLUENCE OF CARBON DIOXIDE UPON THE HEART AND BLOOD VESSELS

The equally marked influence of carbon dioxide upon the circulation has not as yet, or to an equal degree, been exploited for therapeutic purposes. Yet, simultaneously with the modern development of respiration, physiology has produced also observations indicating a powerful influence of carbon dioxide upon the heart. In a long series of experiments,[6] from fifteen to twenty-five years ago, my collaborators and I demonstrated on dogs, under artificial respiration or breathing naturally under a slight pressure of air after the opening of the thorax, a condition verging on tetanus of the heart—in the physiological sense of the word tetanus, that is a fusion of successive beats. This state was effectively counteracted and heartbeats of full amplitude were restored as a consequence of the restoration of a normal, or perhaps slightly excessive, carbon dioxide content in the blood. The lesson of these observations is now generally applied in experiments upon the isolated heart in the Starling[7] heart-lung preparation. It is recognized that the blood for perfusion, in addition to being oxygenated, must also be supplied with a sufficient amount of carbon dioxide to overcome the tendency of an exposed or excised heart to develop an inadequate diastolic relaxation. Otherwise it passes into a continuous systolic state, an incomplete tetanus or cramp of the heart.

Following these observations upon the heart, it was shown in another series of experiments[8] that carbon dioxide may exert an equally strong influence upon the peripheral circulation, and particularly upon the volume of the venous return to the right heart. Clinically this

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effect is best seen as a result of the inhalation of carbon dioxide after a prolonged and extensive surgical operation under open ether anesthesia. The return of blood to the cutaneous vessels, the flushing of the skin, the refilling of the veins previously collapsed, bear at least a superficial similarity to the effects induced by inhalation of amyl nitrite. But the effects, like those of a hot bath and in contrast to amyl nitrite, are more physiological than pharmacological; they are lasting and are accompanied by a restoration of a full strong heart action and a recovery of normal arterial pressure. Never in my experience have there been any symptoms suggesting an overloading of the heart.

Among the various treatments of heart disease, that at Nauheim is the most celebrated. It consists in baths in carbonated water. The good effects, which the treatment is claimed to have, have never really been explained. There is a stimulating action upon the skin, but there is little ground for believing that a slight cutaneous hyperemia can by itself be of much benefit. It is at least possible that the greater part of the benefit sometimes derived from the Nauheim treatment is due rather to inhalation of the carbon dioxide volatilizing from the surface of the bath.

DECREASE OF ANGINA UNDER INHALATION

With these considerations as a physiological background, it has seemed to me justifiable to try, with all due caution at first, the influence of carbon dioxide inhalation upon cases of angina pectoris which are as yet in their earlier stages, but in which moderately severe suffering on exertion is already developing. This is not an emergency treatment, but a therapy for prolonged application. The inhalations are not given during an attack of pain, but at regular times every day, usually before the midday and evening meals, and at bedtime. The patient lies quietly on his back for a few minutes holding over his own face a mask which has a sufficiently large opening to the outside air to offer no resistance to breathing. He is told to keep his mouth open and to breathe deeply rather than rapidly. Then a stream of carbon dioxide gas through a small rubber tube from a cylinder of the pure liquefied substance is fed to the mask. At first the flow is kept small, but as respiration gradually deepens the amount of the gas is increased until at the end of two or three minutes a maximal or nearly maximal depth of breathing is developed. The stimulation is not, however, pushed to the point of increase of rate. This condition is maintained for fifteen or twenty minutes continuously. Then the gas is shut off, and the patient is directed to lie quiet for ten minutes more, so as to avoid the slight giddiness which occurs if he gets up immediately.

It is to be noted that the technic of this inhalation differs markedly from the use of a mixture of oxygen and 7 per cent carbon dioxide, which is best employed for resuscitation from asphyxia. The inhalation used on these heart cases is on the contrary essentially like that applied by Henderson, Haggard and Coburn, and by White after anesthesia and operation.[3] A mixture of oxygen and carbon dioxide is rather expensive, and a cylinder of it is exhausted in a single inhalation; while on the contrary even a small cylinder of liquid carbon dioxide lasts for several weeks of this treatment, so that its cost, aside from the control apparatus, is slight. *But of course pure carbon dioxide should be used only with such an open mask that the small volume of the gas supplied is diluted by the patient's breathing in the relatively large volume of the inspired air.*

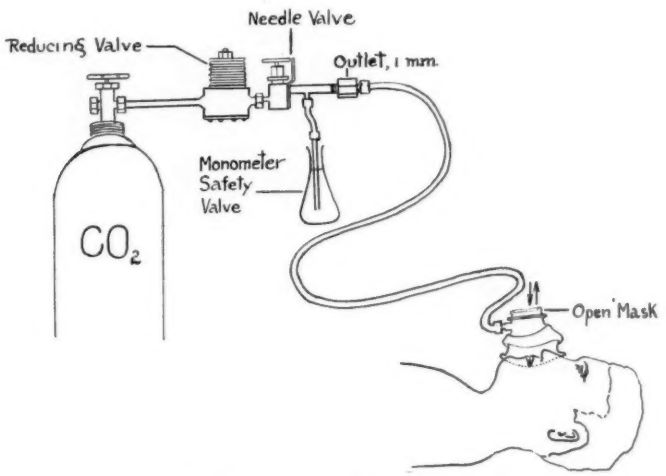

Fig. 1.—Apparatus for administration of inhalation of carbon dioxide with the inspired air. For description and use, see text.

The essentials of the control apparatus employed are (a) an open mask, as above described, and (b) a device for the control of the flow of the gas to the mask, so that by no possibility can the patient receive an excess; it must be fool proof.

For this purpose a water manometer only 100 to 120 mm. long is so arranged that it not only serves as a gauge but also as a safety valve, through which any excess supply of the gas blows off into the air without going to the mask. It is merely a straight glass tube, 5 mm. bore, which extends down for this distance below the surface of water in a bottle, flask or test tube. Between this manometer and the tube leading to the mask is a hole of not more than 1 mm. diameter. Thus the maximum volume of gas that can go to the mask is that which under a pressure of 100 to 120 mm. of water column will pass through a 1 mm. hole. The supply of gas to the manometer and to this milli-

meter hole is controlled either by a finely adjustable needle valve, or better by a McCaa reducing valve and a needle valve, as shown in Fig. 1.* If only the needle valve is used, it has to be frequently readjusted by the person administering the inhalation. If the reducing valve is used also, the flow is so steady that an intelligent patient may manage the entire procedure for himself. This is a distinct advantage in a treatment which the patient may find it necessary to continue one or more times a day for the remainder of his life. For the utmost that can be expected, or even hoped, in regard to such a disorder as angina pectoris is not absolute cure, but a check upon the fundamental conditions, prevention of suffering and prolongation of life.

The effects of this inhalation on the patients thus far treated, as yet only three in number and none with high arterial pressure, have been, in addition to the deeper respiration, as follows: There is a distinct improvement in the color and temperature of the lips and skin, previously rather bloodless or bluish and cold, but becoming warm and pink under the influence of carbon dioxide upon the peripheral circulation. Arterial pressure and the pulse rate are not in appreciable degree increased, although a markedly fuller circulation is evident. The sensation of oppression in the chest, and the pain or "pins and needles" in the shoulder and arm is considerably decreased, and may cease altogether for some hours after the inhalation. After some weeks of daily inhalations the capacity to take such exercise as walking uphill is markedly increased, and the chief difficulty is to prevent the patient from overexerting his partially restored physical capacity.

This is all that it seems justifiable to report in an initial communication on a treatment which will certainly need far more evidence before it can be regarded as of proved general therapeutic value. The cases thus far treated have, however, appeared so much benefited and the technic here described appears to be so safe, that it seems best to put the matter on record, in order that others also may try it for a class of patients for whom there is otherwise little that can be done to relieve or even to delay the development of a peculiarly painful, anxious and hopeless form of invalidism, with an ever-present risk of sudden death from coronary thrombosis.

Mention may also be made here of the effects of this inhalation upon two cases of intermittent claudication in the lower extremities. In both of these cases a marked improvement in the circulation of the ischemic limb was observed under the inhalation, and in one in which the treatment was continued for some weeks there was a distinct cumulative beneficial effect. These cases were studied particularly in the belief that if the pain in angina pectoris and that in intermittent

*An apparatus of this type without the McCaa reducing valve may be obtained from the Foregger Company, 47 West 42nd Street, New York City. An apparatus with the reducing valve from the Mine Safety Appliances Company, Pittsburgh, Pa.

claudication are due to similar local reactions, improvement in both types of cases would tend to support the probability that in both the results are real and not imaginary, either in the patient or in the mind of him who has applied the treatment.

THEORETICAL CONSIDERATIONS

The general conception under which these observations were made was as follows: In a normal person muscular exertion induces no pain either in a limb or in the heart, for the reason that the blood supply is sufficient to afford all the oxygen needed initially in the working parts. This supply of oxygen quickly converts a large part of the fatigue products, especially lactic acid, into carbon dioxide. The carbon dioxide then induces a relaxation of the blood vessels and thus increases the blood supply to the working parts, both heart and limbs. This is the normal reaction to exercise. The healthy man takes a walk or plays an athletic game to improve the oxygenation of his tissues. Thus as Miescher[9] said forty-five years ago: "Carbon dioxide spreads its protecting wings over the oxygen supply of the body."

Quite different is the reaction in a person in whose heart or limbs the blood vessels are sclerotic or constantly contracted. The blood supply and therefore the oxygen supply are insufficient for the initial requirements of exertion. Lactic acid and other fatigue products accumulate; for in the absence of a large supply of oxygen they cannot be burned to carbon dioxide. They tend to induce a cramp of the musculature, cardiac or striated, in contrast to the influence of carbon dioxide which, as I long ago demonstrated experimentally on the heart, promotes relaxation.[6] To do effective work a muscle must be able to relax as well as to contract. From excess of lactic acid and local deficiency of carbon dioxide come the abnormal reaction to exercise, the ischemia and the cramp.

If now a patient who is liable to such an abnormal reaction receives an inhalation of carbon dioxide, still a third form of reaction develops. He experiences the benefits, without the disadvantages, of physical exercise. He makes no exertion. His muscles are at rest, and his heart is put under no additional strain. There is no decrease of the oxygen supply to any part, but rather an increase, for the carbon dioxide inhaled induces a relaxation of the finer blood vessels, a more ample heartbeat, and a fuller circulation. The balance of supply and demand for oxygen in the tissues is thus distinctly improved and the tendency to cramp is diminished. Furthermore as the treatment is repeated day after day the blood vessels and the heart muscle, under the influence of an essentially normal physiological agent and an essentially normal reaction, gradually acquire and retain a state of decreased habitual strain and more normal behavior. Along these lines

we may figure to ourselves why and how inhalations of carbon dioxide may exert a beneficial effect both immediate and to some degree lasting.

In support of this general conception mention may here be made also of the extraordinary observations which were reported by the late Dr. A. S. Loevenhart[10] in which he found that inhalation of carbon dioxide administered to cases of catatonia caused a temporary restoration of mental responsiveness. The simplest explanation of the results in these cases is to postulate an habitual contraction of blood vessels in the brain of the catatonic patient and to assume that the influence of carbon dioxide upon these vessels is similar to that upon the peripheral circulation elsewhere in the body. The effects of overbreathing in inducing, and of oxygen and carbon dioxide in temporarily inhibiting, fits in epilepties[11] are also suggestive of a similar conception.

Finally I have pleasure in acknowledging my indebtedness to my colleague, Dr. George Blumer, for the opportunity to work on one of the cases here reported, and to Dr. Samuel C. Harvey for two of the others. Investigations on the experimental side of this general problem are now being published from Dr. Harvey's laboratory, and further investigations upon patients are to be conducted in the clinic here.

CONCLUSION

Daily inhalations of carbon dioxide appear to offer a possibility of considerable amelioration of the crippling effects and suffering in cases of angina pectoris and also of intermittent claudication.

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Department of Clinical Reports

A CASE OF PATENT DUCTUS ARTERIOSUS WITH PRIMARY BACTERIAL PULMONARY ENDARTERITIS*

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CLINICAL OBSERVATIONS

A 15 year old white girl entered the Vanderbilt University Hospital October 4, 1929. She complained of cough, weakness, and loss of weight of ten weeks' duration. In July, 1929, she suddenly experienced severe pain in the lower part of the left chest, which was increased by respiratory movements and later was associated with chills, night sweats, fever, cough and blood tinged sputum. She was in bed five weeks with this illness, during which she lost twenty pounds. At the end of this time there was a short remission after which she was forced to return to bed where she remained until her admission to the hospital in October.

The past history revealed that she had been a normal healthy child who was capable of the normal exertions of other children of her age. At no time had she been cyanotic, dyspneic, or edematous. She had not had rheumatic fever or chorea.

The physical examination on admission revealed striking emaciation, pallor and generalized muscular weakness. Her temperature was 102° F. and pulse rate 120 without much increase in respirations. The heart was beating forcibly as well as rapidly. The rhythm was regular. The cardiac measurements were as follows: left border 10 cm. from the midsternal line in fifth interspace, right border 3.3 cm. in the fourth interspace. There was also a demonstrable increase in the cardiac dulness in the left first and second interspaces measuring 5.3 cm. to the left of the midsternal line. In the pulmonic area there was a blowing continuous murmur with accentuation of the systolic phase associated with a faintly palpable thrill. The pulmonic second sound was loud and the shock could be palpated. The percussion note was impaired, and there was a moderate number of moist râles over the left lower lung. The spleen was not palpable at this time. She had no petechiae, edema, clubbing or cyanosis.

The laboratory findings showed red blood cells 2,710,000, hemoglobin 50 per cent, white blood cells 15,780. Differential: 79 per cent neutrophiles, 16 per cent small lymphocytes, 0.5 per cent eosinophiles, 5.5 per cent large monocytes, 1 per cent unclassified. Urinalysis showed a persistent albuminuria without red blood cells. Blood cultures revealed streptococcus viridans on many different occasions.

On the basis of these findings the diagnosis of patent ductus arteriosus with a superimposed nonhemolytic streptococcic endarteritis of the pulmonary artery near the orifice of the duct was made. This diagnosis was made on the evidence, both clinical and bacteriological, of subacute bacterial endocarditis plus the signs of a congenital cardiac anomaly, namely a patent ductus arteriosus. The lung signs were interpreted as due to pulmonary infarcts. It was thought that the vegetations were on the pulmonary side of the ductus on account of the absence of petechiae and hematuria, and because of the pulmonary infarcts. Also there were no murmurs to suggest that the mitral valve was diseased at this time.

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Her course, as one would expect, was progressive, but she lived for six and a half months after her first admission or eight and a half months after the onset of her illness. During the last six and a half months of her life she was admitted to this hospital three different times. During these periods she received a total of thirteen blood transfusions which brought about a transient relief from the symptoms of anemia.

During the first admission she improved definitely. Although she gained eight pounds and was able to be up part of the time, the fever and tachycardia continued. The results of the second and third admissions were not so gratifying. Each time she was more anemic and responded less to transfusions. Blood cultures always contained streptococcus viridans. Late in the illness she began to show petechiae and hematuria, and the spleen became palpable.

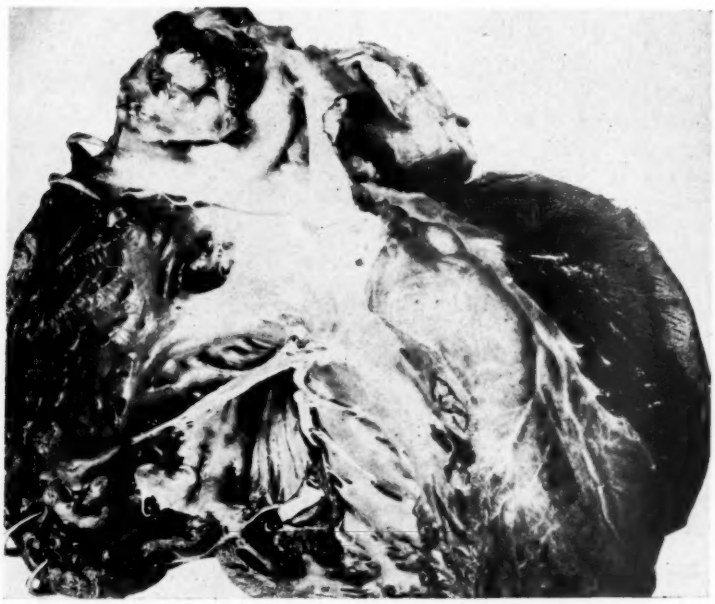

Fig. 1.—The anterior flap of the right ventricle has been turned back so that the pulmonary artery is exposed in the upper left hand portion of the photograph. Attached to the orifice of the ductus arteriosus approximately one centimeter above the normal thin pulmonary valves, is the huge vegetating thrombus which almost occludes the pulmonary artery. The extensive overgrowth of this thrombus by endothelium is obvious from the photograph. The depression immediately below the thrombus represents the aneurysm described at autopsy. In the lower portion of the ventricular cavity the normal tricuspid valve is visible. The ventricular hypertrophy and dilatation are obvious.

She was not frequently observed during the last month of her life and died at her home on April 17, 1930. During the last few days she developed anasarca, profound anemia, and coma.

Notes of the post-mortem examination, which was restricted to the chest and the removal of the heart, are as follows:

"The lungs are riddled with nodular, reddish, discolored areas, some of which are fluctuant. A portion of the left lower lobe anterolaterally is widely adherent to the chest wall by dense fibrous marginal adhesions and the underlying lung is fibrotic.

"The heart weighs 290 gm. Both left and right ventricles are enlarged. The pulmonic valve is entirely normal. The pulmonary arteries beyond the main bifurcation are smaller than normal, measuring approximately 0.75 cm. in diameter. The

ductus arteriosus is widely patent and cylindrical, measuring 1.5 cm. in length and 0.5 cm. in diameter. The aortic opening is easily probed but the pulmonary opening is closed by a large greenish-gray, friable, firmly adherent vegetation lying in the pulmonary artery and invading the pulmonic orifice of the ductus. This mass of vegetation measures 2.5x1.5x1.5 cm. and almost completely occludes the pulmonary artery at its bifurcation. A small aneurysmal dilatation of the pulmonary artery 1 cm. in diameter is present about 0.5 cm. heartward from the vegetation.

"The mitral valve measures 7 cm. Scattered along its free edge are numerous grayish-red, friable, loosely but definitely adherent vegetations. On its septal cusp there is present a large vegetative mass 0.5x1.0x0.75 cm.

"The aortic valve is entirely normal. There is no stricture of the aorta or of its isthmus. The left ventricular myocardium measures 1.25 cm. at the apex and 1.75 cm. at the base. The cavity is one and a half times its normal size. The right ventricular wall measures 0.75 cm. at its apex and 1.25 cm. at the base. Its cavity is enlarged to twice its normal size.

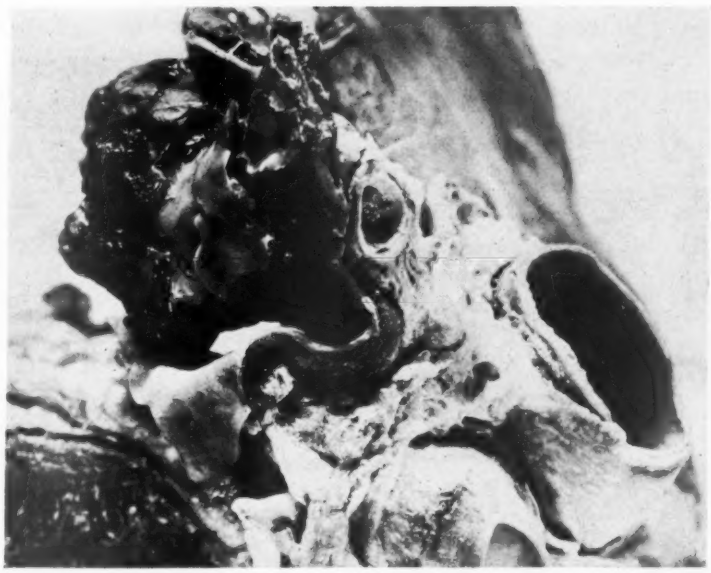

Fig. 2.—A "close up" photograph of the pulmonary artery and the ductus. Here again the huge vegetation is seen in the upper left hand portion of the photograph. Immediately to its right the patent ductus, its lumen plugged by a portion of this thrombus, is visible. The apparent puckering of the intima of the ductus is a fixation phenomenon.

"*Microscopic Notes:* The superficial vessels of the epicardium are markedly congested and the tissues widely hemorrhagic. Extensive infiltration by polymorphonuclear leucocytes along the trabeculae is evident. The myocardium of both ventricles is edematous. The muscle cells are large with hypertrophic nuclei, and of these some are fragmented. Focal microscopic areas occur throughout the substance of both ventricles in which the coronary arterial branches are thrombosed by hyalinized emboli. In two of these thrombi coccoid bacteria are demonstrable. The surrounding muscle cells are hyalinized, eosinophilic, and together with adjacent interstitial tissue, markedly edematous, and infiltrated with polymorphonuclear leucocytes. The muscle cells at the periphery of these necrotic areas are swollen by myriads of fat vacuoles.

"The pulmonic vegetation consists of a central core of fibrous tissue from the periphery of which the thrombus is undergoing rapid organization. The vegetation

covering the central fibrous core consists of laminated fibrin bands heavily infiltrated with polymorphonuclear leucocytes and bordered by a massive zone of bacteria which extends in huge colonies into the depth of the thrombus. The bacteria are gram-positive streptococci.

"*Anatomical diagnoses*: (1) Subacute bacterial endocarditis, viridans, affecting the pulmonary artery (ductus orifice) and mitral valve; (2) Congenital cardiac anomaly, patent ductus arteriosus; (3) Stricture of terminal pulmonary arteries; (4) Pyemia, subacute bacterial endocarditis (viridans); (5) Pulmonary infarcts, septic; (6) Myocarditis, focal, acute, septic emboli; (7) Cardiac hypertrophy and dilatation, biventricular."

DISCUSSION

Patency of the ductus arteriosus is not at all rare, but there are extremely few cases in which the duct seems to be the original seat of

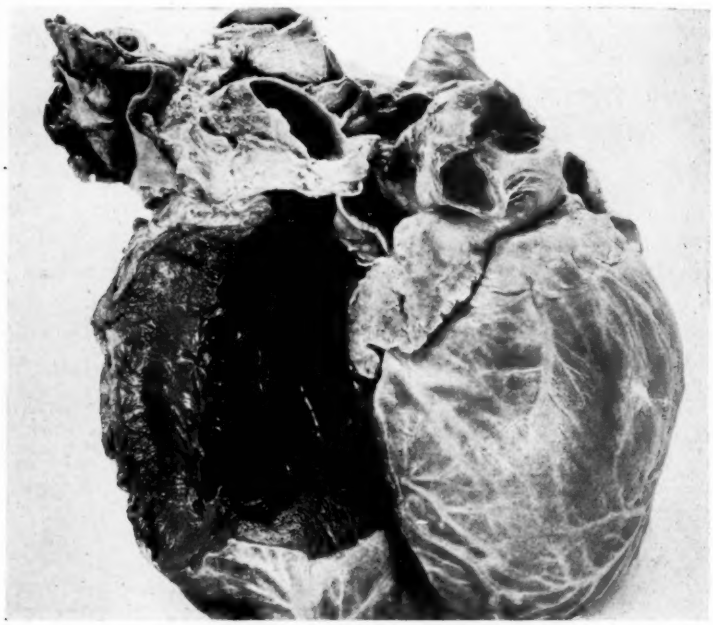

Fig. 3.—The gross photograph of the left side of the heart. The pulmonary artery and patent ductus are visible in the upper left hand field of the photograph. The rather marked hypertrophy of the left ventricular wall is obvious in this photograph.

a vegetative endarteritis. Hamilton and Abbott[1] in 1914 reported such a case in a girl of 19 years. In their case the vegetations were located around the pulmonary orifice of the duct. There were numerous embolic abscesses in both lungs, and pneumococci were found in blood culture, in the vegetations and in the embolic abscesses. Coarctation of the aorta was also present. Schlaepfer[2] in 1926 reported a case in a boy, aged 8 years, in which there was an organizing and acute arteritis of the pulmonary artery and ductus arteriosus with thrombotic occlusion of both the duct and the pulmonary bulb. There were multiple pulmonary and splenic infarcts, and the streptococcus

viridans was found in blood culture. Krzyszkowski[3] in 1902 reported a case in a female, aged 17 years, in which a vegetation was found on the wall of the pulmonary artery just above the pulmonary valves. There was an aneurysmal dilatation of the pulmonary artery opposite the orifice of the ductus arteriosus, and pulmonary infarcts were present. A bacteriological diagnosis in Krzyszkowski's case was not made. The literature of pulmonary endarteritis has been reviewed by Hamilton and Abbott[1] and by Schlaepfer.[2] In all there are nineteen cases of pulmonary endarteritis, but of these sixteen showed one or more valvular lesions in association with the pulmonary endarteritis.

This case is one in which, although the pulmonary endarteritis is not the only cardiac lesion, the pulmonary artery can be shown to be the

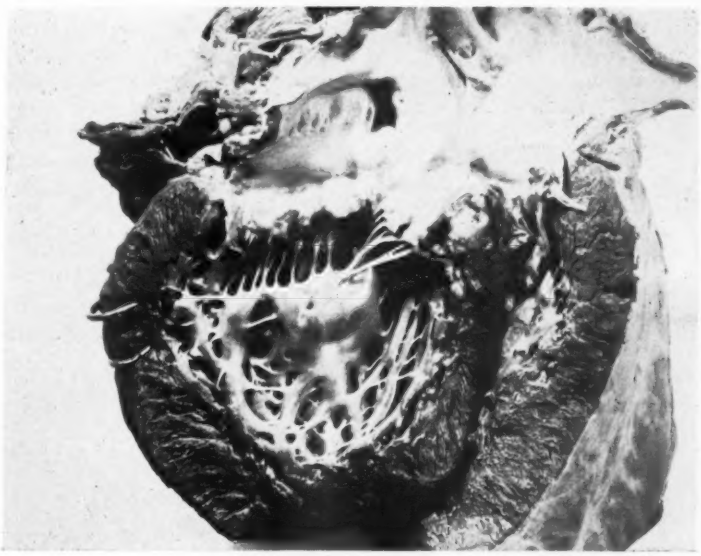

Fig. 4.—A view of the left ventricular cavity. Extensive recent friable thrombi are adherent along the auricular surface of the mitral valve. The closed foramen ovale is visible above.

primary seat of disease. This is demonstrated by the absence of mitral murmurs at the time the patient had conclusive evidence of right sided bacterial endocarditis, the absence of peripheral embolic phenomena until late in the illness and the presence from the beginning of signs which were interpreted as pulmonary infarcts. In addition the pathological study indicates that the pulmonary endarteritis was an older and more advanced lesion than the mitral lesion.

The findings which led to the diagnosis of the pulmonary endarteritis were: a continuous blowing murmur in the pulmonic area with accentuation of the systolic phase; a loud pulmonic second sound and a faint thrill in the same area; an extension of the cardiac outline to the left in the first and second interspaces which was shown both by

percussion and x-ray examination; pulmonary infarcts without peripheral emboli and the occurrence of Streptococcus viridans in blood cultures.

SUMMARY

A case of pulmonary endarteritis, with the vegetation superimposed upon the wall at the orifice of a patent ductus arteriosus, which was diagnosed clinically six and a half months before death and confirmed by autopsy, is reported. Although the mitral valve was also the site of vegetations, the pulmonary endarteritis is shown to be the primary lesion.

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PERICARDIAL EFFUSION OF UNKNOWN ETIOLOGY NECESSITATING REPEATED PARACENTESIS*

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CASE REPORT

The patient was a boy nine years of age, born of Italian parentage in the United States. On October 19, 1927, he was brought to the Clinic by his parents, who stated that during the preceding month he had complained of occasional colicky pain in the stomach unaccompanied by nausea or vomiting. The bowel movements had been perfectly regular. He also complained that during the preceding two weeks he had been short of breath on exertion, and during this period his mother had noted coldness of the extremities and a bluish discoloration of the lips and ears. His appetite had been poor during the preceding month, and he had lost some weight.

The patient's past illnesses included measles and occasional colds and sore throats. Tonsillectomy and adenoidectomy were performed in 1923. In the spring of 1927 the patient had two attacks of bronchitis, and in the opinion of his parents he had not regained his normal health since that time.

Examination.—The patient was a moderately well-developed and well-nourished boy four feet in height and weighing 53 pounds. The ears and the mucosa of the lips showed a marked cyanotic tint, and there was a mottled cyanotic discoloration of the skin of the chest, abdomen and lower extremities. The boy did not appear to be in distress and there was no increase in the respiratory rate. His temperature was 98°, pulse rate 108, and blood pressure 90/64 mm.

Examination of the chest revealed marked bulging on the left side rendering it asymmetrical. Respiratory movements were practically absent on this side, and there was dullness on percussion over the entire left chest anteriorly, with the exception of the region superior to the second costal cartilage, especially in the axillary area. Posteriorly there was marked diminution of resonance over the lower two-thirds of the left lung. Breath sounds were indistinct over the entire left lung and over the base of the right lung. No adventitious sounds were heard. The external limit of cardiac dullness in the left fifth interspace was 10.5 cm. from the midline and 5.5 cm. in the right fourth interspace. The heart sounds were regular and rhythmical but very indistinct. There was a well-marked pulsus paradoxus. The edge of the liver was palpable two inches below the costal margin in the right midclavicular line. A small amount of free fluid was observed in the peritoneal cavity. There was no demonstrable enlargement of the spleen.

A diagnosis of pericardial effusion was made, and in view of the evidence of pressure, aspiration was carried out through the left fourth interspace, one inch beyond the sternal margin. Approximately 1000 c.c. of a clear, slightly amber fluid were removed without difficulty. By the time the aspiration was complete, the cyanosis was gone, the liver edge was just palpable under the costal margin, and the patient announced himself feeling well and hungry. He was put to bed, and given large doses of salicylates. Three weeks later the effusion recurred, and again 1000 c.c. of fluid were removed. Subsequently, over a period of one year, quantities of fluid varying from 500 to 1800 c.c. were aspirated at intervals of

*From the Cleveland Clinic.

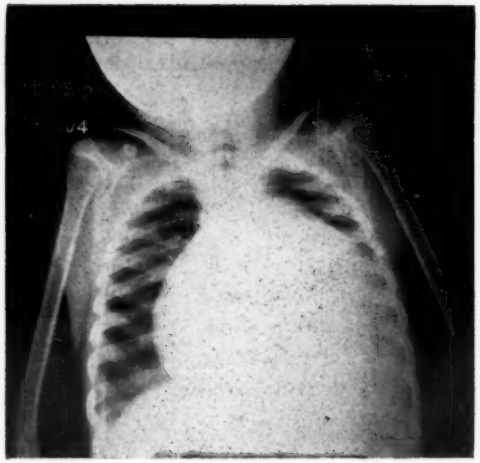

Fig. 1.

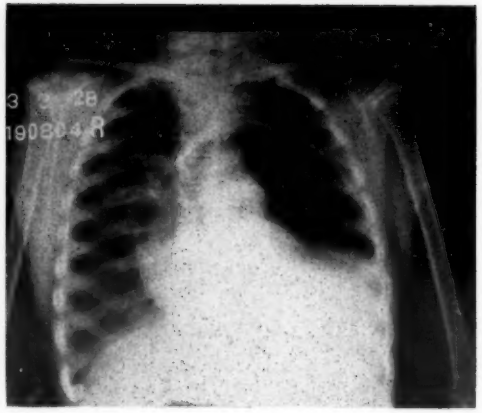

Fig. 2.

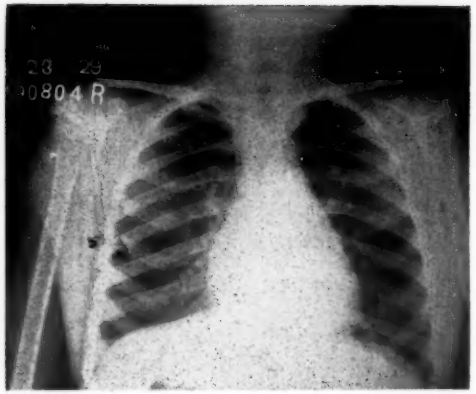

Fig. 3.

Fig. 1.—Roentgenogram showing a case of marked pericardial effusion which obliterated the heart shadow.
Fig. 2.—Roentgenogram of chest, showing pneumopericardium. Note the fluid level.
Fig. 3.—Roentgenogram of chest taken six months after cessation of the effusion.

about ten days to two weeks. The effusion ceased in November, 1928. All aspirations were performed through the fourth or fifth interspaces, right or left, immediately adjacent to the sternum or one inch from it.

Laboratory Findings.—When the patient was admitted to the hospital the red blood cells numbered 4,350,000, the white blood cells 8,000, and the hemoglobin was 80 per cent. The differential count showed 58 per cent of polymorphonuclear cells and 43 per cent of lymphocytes. Throughout the course of treatment there was little variation in these figures. The urine usually was normal, although at times it contained a trace of albumin. The blood Wassermann and Kahn tests were repeatedly negative, as were the von Pirquet and intracutaneous tuberculin tests. Roentgenograms of the chest on numerous occasions showed the typical picture of a large pericardial effusion.

The aspirated fluid was clear and straw-colored, and on standing showed a few strands of fibrin. The specific gravity of this fluid was 1.016 to 1.018. It contained only from ten to twenty cells per cubic millimeter. These were chiefly endothelial cells with an occasional lymphocyte. Repeated cultures on various types of media were invariably negative, with the exception of one tube in which an organism of the colon group was found, obviously a contamination. On repeated occasions guinea-pig inoculation was negative for tubercle bacilli.

Course.—Many types of medication were tried. The patient was placed in bed and kept there for four months, after which time he was allowed to be up and take exercise in restricted amounts. He was given several toxic doses of salicylates and courses of Fowler's solution without any obvious improvement being noted. Novasurol was used on three occasions, after preparation with ammonium chloride, but aside from the fact that the interval between aspirations was increased by a few days, no benefit was noted. Generalized ultraviolet-light treatment was given and general supportive measures were instituted. A pneumopericardium was produced, 500 c.c. of air being introduced at one time. This was absorbed entirely within five days. Restriction of fluids was attempted but the pericardial effusion persisted despite apparent dehydration. The suggestion that some irritating fluid be introduced into the pericardial cavity was advanced on several occasions, and finally after forty-four aspirations had been necessary, 10 c.c. of a one-per-cent aqueous solution of aniline gentian-violet was injected, as suggested by Dr. A. R. Barnes of The Mayo Clinic and others. In twenty-four hours this was followed by fever, the temperature rising to 102.5° and the pulse rate to 130. There were evidences of large deposits of fibrin within the pericardium, and the symptoms subsided in a week. Four subsequent aspirations were necessary, decreasing amounts of fluid being drawn. The last aspiration was performed four weeks after the injection of the gentian-violet solution. Examination of the fluid removed after this injection proved it to be sterile and to contain a large quantity of fibrin and numerous polymorphonuclear leucocytes, as well as many red blood cells.

RESULTS

The striking feature of the case was the complete change in the patient's condition after the fluid had been removed by mechanical means. The formation of the fluid had been heralded by anorexia, lack of energy, a full feeling in the chest and abdomen, and frequently pain referred to the supraclavicular areas on each side. Paracentesis invariably gave immediate relief. During the year in which the patient was treated he increased in height and gained in weight, irrespective of the variations caused by the accumulation of fluid. After injection of the gentian-violet solution he experienced considerable

pain which was referred to the precordia but more especially to the shoulder areas, chiefly on the left side. After the cessation of fluid formation there was some persistent hepatic enlargement which gradually decreased until finally the liver returned to normal size. Cardiac examination now shows a normal-sized heart, with a regular, normal rate, and free from murmurs and evidences of synechiae pericardii. The patient is absolutely symptomless, and is living a normal life.

COMMENT

The etiological factor in the persistent pericardial effusion in this case can only be surmised. The absence of general constitutional reaction, the failure of specific drug therapy and the negative results of bacteriological investigation as well as the favorable outcome render it unlikely that at any time was an organism actually present in the effusion.

In the absence of any apparent cause it seems possible that the effusion was produced by some mechanical factor or pressure upon the inferior vena cava. Repeated studies by x-ray pictures failed to reveal any tumor of the thorax, pericardium or mediastinal structures, and the theory of a partial venous stasis in this locality cannot be confirmed. Theoretically its location would have to be within the very short course of the intrapericardial or superdiaphragmatic portion of the inferior vena cava. In experiments on animals Carl Rohde was unable to cause an effusion of pericardial fluid by placing stenosing ligatures on this vessel.

SUMMARY

A case of chronic pericardial effusion is presented which seems to be unique in the amount of fluid produced. The effusion probably was the result of some mechanical interference with the circulation of blood in the inferior vena cava or with the absorption of pericardial fluid. A chemical inflammation of the pericardium apparently resulted in relief of the etiological factor.

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PAROXYSMAL CARDIAC PAIN IN A PATIENT WITH RHEUMATIC HEART DISEASE

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PAROXYSMAL cardiac pain occurring in patients with rheumatic heart disease is infrequent. The case here described is that of a young adult who has been a patient of the First Medical Division of the New York Hospital and is reported, not only because it presents an unusual syndrome, but also for the reason that the pain, which was the first symptom of heart disease, has gained increasing dominance over thirteen years of exhaustive treatment.

CASE REPORT

J. S., a female, aged 26 years, was admitted to the hospital for the sixth time on October 22, 1930. In her previous history there was measles at the age of 2, confinement to bed for a month a few years later with whooping-cough, chicken-pox at 9, and 5 weeks in bed with bronchitis at 11 years. The pain of which she complained on admission was first experienced 13 years before at the age of 13 when, after jumping rope with playmates, she felt chilly, had no appetite for supper, and while relieving a thirst with water, was seized with a knife-like pain in the apical region of the precordia and a rapid beating of the heart; these symptoms continued for about 2 hours. Then followed a period of a month in bed with fever and pain in all of the joints. She attended school for a year, at the end of which occurred a second attack similar to the first. For 5 years she was afflicted with seizures of precordial pain, varying both in frequency and duration, until at the age of 18 she entered the hospital, presenting fever, joint pain, tonsillitis, and spontaneous precordial pain; the tonsils were removed. Two months later she was again admitted to the hospital because the pain was more frequent, especially at night. Rest in bed seemed to lengthen the intervals between the paroxysms. At about this time the pain first began to radiate from the apical region of the precordia to the right shoulder and entire right arm. Soon the attacks, occurring chiefly in the night, again became more frequent and necessitated a third period of rest in the hospital. After her discharge, fever and pain in the joints reappeared, the third invasion. The following year she again sought hospitalization and the rest in bed which had previously diminished the frequency and severity of the seizures. For the next four years she lived at home, attending the hospital out-patient clinic, and, with the exception of a few days during which her ankles were swollen and painful and of the continuous paroxysms of pain, she remained well. At the end of this period hospitalization was again required, for she was having intense pain at least 4 times a day. The pain at this time was so severe that it was finally decided to attempt to give relief by blocking of the nerve roots. The first to the eighth thoracic nerves on the left side were injected with alcohol by Dr. Swetlow,* and although after this procedure the attacks lessened

*Nerve injections were made on two occasions, the second to the seventh left thoracic roots the first time and the first, second, and sixth to the eighth left thoracic ganglia later. Following each, slight diminution of sensation to cotton and pin-point were detected in the skin of the left thorax. After the second blocking, ptosis, enophthalmos, and myosis of the left eye appeared, and the left arm felt subjectively and objectively warmer than the right; this phenomenon remained for a month.

in their frequency and intensity, it is probable that rest in bed alone was responsible for this result, as it had been before. If the blocking of the nerves had exerted any beneficial effect, it had disappeared 6 months subsequent to the last injections, because at that time the seizures of cardiac pain had increased not only in severity, but also to the number of 15 to 20 in the 24 hours, the majority taking place at night. The foregoing is a sketch of the history previous to the patient's sixth and most recent admission to the hospital.

A description of the syndrome as it has occurred most recently will now be given, first from the subjective standpoint of the patient, and then from the objective point of view of the observer. Precipitating causes of the paroxysms are numerous and varied. Primarily there is muscular exertion, such as walking rapidly and climbing stairs. Second, there are sudden changes in temperature, as produced by a cold draft of air and the swallowing of cold water. Third are the emotional reactions, when "my insides take a sudden jump." A knock on the door, a disagreement, an unpleasant dream, and exciting moving-pictures have all played their painful part. Finally there are those causes which we cannot name. Her field of activity, both physical and mental, is therefore greatly limited. The first sign of an attack is a sharp knife-like pain in the apical region of the precordia which radiates to the area of the third right intercostal space near the sternum and to the right shoulder and entire right arm. Shortly after the onset of the pain the heart pounds very rapidly. Accompanying these symptoms are a feeling of compression in the chest, shortness of breath, "lifelessness" of the right arm, weakness, dizziness, sweating, and great fatigue; after the seizure has spent itself the areas of pain remain sore. The patient believes that nitroglycerine and amyl nitrite, chiefly the latter, shorten somewhat the paroxysms, which last over periods varying from 3 minutes to 7 hours. The most promising form of treatment is prolonged rest in bed, which lessens both their frequency and their intensity. To the observer of these attacks the picture is one of a very pale young woman in a semirecumbent position in bed, arms limp at her sides, rolling frequently from side to side as if to shake off the pain which is clearly revealed in her face. There is rapid breathing and profuse perspiration. The neck bulges with each pulsation of the carotids and gives sufficient evidence of the tachycardia which is present, a rise of 48 beats to the minute above the normal in one instance. Blood-pressure determinations reveal an increase of tension, a rise of 30 points in the systolic pressure above the normal on one occasion, with no alteration in the diastolic. An electrocardiographic tracing taken during a seizure demonstrates a sinus tachycardia of 116 per minute, and a P-R interval prolonged to 0.22 seconds. There is a large Q-wave in Lead III and the T-wave is diphasic in Lead I. Another record obtained immediately after the subsidence of the paroxysm discloses frequent premature ventricular contractions and an inverted T-wave in Lead I.

Physical examination reveals a young adult female, Irish in origin, of excellent development and nutrition, pale of skin and lips, preferring the semirecumbent position in bed, but not orthopneic, throbbing slightly with each heartbeat, breathing quietly, with normal temperature, and not appearing ill, but showing in her face and mental attitude a resignation to a life of pain. The tissues over the carotids pulsate violently with the arteries. A heaving impulse may be seen and felt over almost the entire left chest, but no shocks or thrills can be detected. On auscultation over the precordia one hears in the region of the apex two murmurs: the first, entirely replacing the first heart sound, is of moderate intensity, blowing in quality, of moderate duration, and systolic in time; the second murmur is of moderate intensity, rumbling in quality, of short duration, and presystolic in time. Over the base are heard two murmurs: the first, most distinct in the first right intercostal space near the sternum and transmitted upward into the neck, is of loud intensity, rumbling in quality, of long duration, and systolic in time; the sec-

ond murmur, most distinct in the second left intercostal space near the sternum and entirely replacing the second heart sound, is of loud intensity, blowing in quality, of moderate duration, and diastolic in time. The average resting rate of the heart is 84 per minute and the rhythm regular, but subject to premature ventricular contractions. An x-ray plate of the thorax reveals an enlarged heart, the greatest width to the left of the midline being 11.8 cm. and to the right 4.5 cm., the internal transverse diameter of the chest measuring 25.5 cm. Râles may be detected occasionally over the lung bases. The liver cannot be felt. There is a Corrigan pulse, a capillary pulse, and a pistol-shot sound on auscultation over the femoral artery. Blood-pressure readings taken in the absence of pain average 165 systolic and 51 diastolic. Edema has never been observed in the entire course of her illness. Electrocardiograms taken at periods when there was no pain show normal sinus rhythm, a wide and large P-wave, a wide and notched QRS group, inversion of the T-wave in Lead I, and a P-R interval prolonged to 0.22-0.24 seconds. These abnormal physical findings lead to the following diagnosis:

A (etiological). Rheumatic fever, inactive.

B (anatomical). Enlargement of the heart; cardiac valvular disease, aortic insufficiency and stenosis, mitral insufficiency and stenosis.

C (physiological). Regular sinus rhythm interrupted by periods of premature ventricular contractions and paroxysmal tachycardia; auriculoventricular partial heart-block; hypertension; anginal syndrome.

D (functional capacity). 2 b .

Of outstanding significance in this case of rheumatic heart disease is its most prominent symptom—paroxysmal cardiac pain, which not only marked the onset of the disease, but also has persisted with increasing vigor for thirteen years against a formidable array of procedures comprising the removal of focal infection, rest, nerve blocking, digitalis, quinidine, salicylates, analgesics, sedatives, antispasmodics, and vasodilators.

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ACQUIRED RHEUMATIC PULMONIC STENOSIS AND INSUFFICIENCY*

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AND
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ACQUIRED rheumatic lesions of the pulmonary artery of sufficient severity to give clinical signs are very uncommon. There are exceedingly few cases reported in the literature where a diagnosis was suspected during the life of the patient and proved at autopsy.[1, 2, 3] The following case is of particular interest, not only because of its unusual clinical manifestations, but also because of the typical radiographic findings associated with insufficiency of the pulmonary artery.[4]

REPORT OF CASE

M. R., a female, aged 22 years, was admitted to the Montefiore Hospital on April 29, 1928, and died on May 5, 1928. Her chief complaints were severe dyspnea, palpitation of the heart and swelling of the abdomen and lower extremities.

Previous Illness.—The patient became ill for the first time in January, 1921, and remained in bed for the next four weeks because of "inflammation of the lungs." She returned to work the following summer but was unable to walk. She became easily fatigued and unable to climb a single flight of stairs without stopping several times in order to "catch her breath." She entered the Bellevue Hospital where she remained at first, for three months, and during the subsequent two years she had to be readmitted to this institution on five separate occasions because of recurrent symptoms of shortness of breath, palpitation of the heart, precordial pain and swelling of the lower extremities.

In May, 1921, on her second admission to Bellevue Hospital, the patient suffered a hemiplegia. At that time, physical examination revealed a fairly nourished and fairly well developed young woman who was extremely short of breath. She showed a complete hemiplegia of the right side of the body. Her cheeks, lips and ears were very cyanotic. The superficial vessels of the neck were distended. There was marked pulsation of the carotid vessels. The heart was enlarged downwards and to the left, the apical impulse being in the fifth intercostal space in the anterior axillary line. In the second intercostal space, the left border of the heart percussed 6 cm. to the left of the midsternal line. There were a loud systolic and long rumbling diastolic murmur both best heard over the fifth intercostal space near the midclavicular line. A prolonged, loud diastolic murmur was audible over the second intercostal space to the left of the sternum. The murmur was well localized to this region but could also be heard distinctly over the upper left chest posteriorly. The pulses were equal and regular. The blood pressure was 120/80 mm. The lungs were clear, the liver edge was palpable two fingers below the costal margin. There was marked swelling of the lower extremities.

*From the Medical Division of the Montefiore Hospital for Chronic Diseases, New York City.

X-ray examination at that time is summarized as showing "an enlarged heart with a straightened left border and a small bulge of the pulmonary artery."*

Because of the absence of peripheral signs of aortic insufficiency such as a Corrigan pulse, a low diastolic blood pressure and capillary pulsation, a diagnosis of pulmonary insufficiency was made at this time in addition to the evident stenosis and insufficiency of the mitral valve.

With adequate rest and the judicious use of diuretics, the patient was able to leave the hospital in a fair condition within four weeks after admission. However, within the next few months, she became progressively worse and because of the extreme shortness of breath and palpitation of the heart, she had to be readmitted to this institution several times in the succeeding two years. That was in 1921.

The patient remained at home from 1924 to 1927. In the winter of 1927, she entered the Jewish Hospital of Brooklyn in a very critical condition. In the two or three weeks prior to her admission to that institution she was having dizzy spells, vomiting, headaches, and a progressive increase in the swelling of the legs and ankles.

On examination, she was found to be extremely dyspneic and orthopneic and showed signs of dropsical effusion in the abdominal cavity with marked generalized swelling of practically the entire body. Her heart rhythm was totally irregular, and averaged 120 beats per minute, there being a pulse deficit of 28. The liver was now at the level of the umbilicus and was pulsating. The unusual clinical features were the wide areas of pulsation in the second and third intercostal spaces to the left of the sternum. In this region, the left border of the heart percussed near the anterior axillary line. A short, rough systolic thrill with a sharp diastolic shock could be felt over the second intercostal space near the midclavicular line. The apex of the heart presented a loud systolic murmur and a short rough rumbling diastolic murmur.

The x-ray film of the chest taken on January 31, 1927, revealed the heart shadow to be somewhat pyramidal in contour, with a rounded apex, and decidedly broadened inferiorly with displacement towards the left. The findings were considered atypical, and from the radiograms alone it was impossible to diagnose the type of valvular defect. The lung fields were clear with the exception of the right base which presented slightly increased markings and change in appearance when the patient was in the erect posture as compared with the prone position, suggesting the presence of a small amount of fluid.†

Because of the unusual clinical findings with the marked enlargement and pulsation of the heart in the second intercostal space, in the absence of large quantities of fluid in the right pleural cavity, a diagnosis was ventured of aneurysm of the pulmonary artery associated with chronic valvular heart disease of the mitral orifice, complicated by a relative tricuspid insufficiency.

Between her discharge from the Jewish Hospital of Brooklyn and her admission to the Montefiore Hospital, the patient had one paracentesis abdominalis.

Physical examination at the Montefiore Hospital on April 29, 1928, revealed an intensely dyspneic and orthopneic young woman who was acutely ill. Her face showed pale cyanosis in marked contrast with the intense cyanosis of her hands and feet. She was in a sitting posture but her superficial and deep neck veins were markedly distended, the latter showing a ventricular form of venous pulse. There was a slight deformity of the anterior left side of the chest with bulging of the left half of the sternum and the costosternal junctions in the region of the second, third, fourth, and fifth intercostal spaces. The apical impulse of the heart was in the sixth intercostal space in the anterior axillary line. There was a marked

*We wish to express our thanks to Dr. M. J. Thornton of Bellevue Hospital for the privilege of this report.

†We wish to express our thanks to Dr. John A. Daugherty for the privilege of using this report.

precordial heave with a diffuse pulsating wave from the third to the fifth intercostal spaces. This part of the chest was painful to touch. The area of cardiac dullness was enormously enlarged to the left reaching the anterior axillary line in the second and third left intercostal spaces. A marked systolic pulsation over the second intercostal space extended 12 cm. to the left of the midsternal line. Over this region but nearer to the sternum, there was a marked systolic thrill felt best with the patient in a sitting posture and leaning slightly forward and to the left.

The apical region of the heart presented a loud systolic and a short, rough, rumbling diastolic murmur, while the basal region of the heart on the left side in the second intercostal space revealed a short, rough systolic murmur with a loud prolonged diastolic murmur. P_2 was not audible. The heart rate was totally irregular, and there was clinical and graphic evidence of auricular fibrillation. Both pleural cavities revealed the presence of small quantities of fluid. The liver edge was at the level of the right iliac crest, and the legs were extremely swollen. There was a small quantity of fluid in the abdominal cavity.

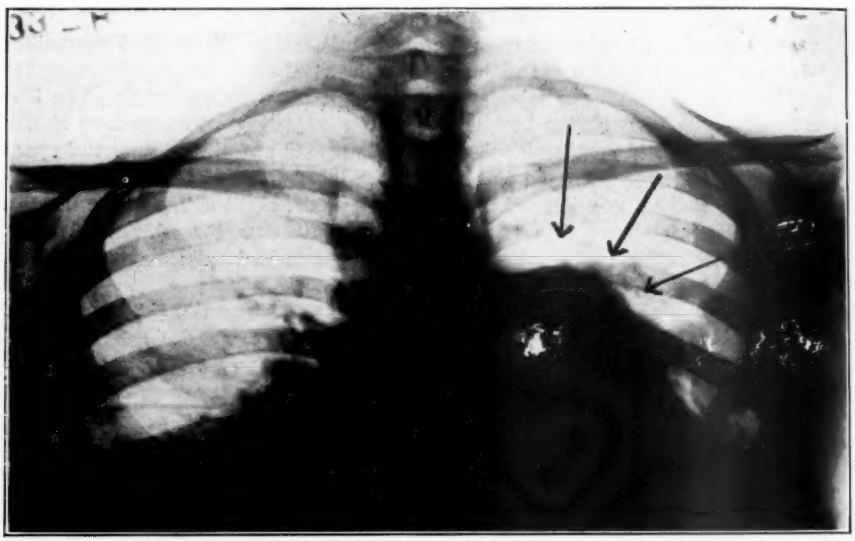

Fig. 1.—Roentgen-ray examination of the chest on admission to the Montefiore Hospital revealed a moderate amount of fluid in the right pleural cavity. The heart was enlarged and rotated so that the aortic knob was not visible in the anteroposterior position. There was an unusual dilatation of the pulmonic artery which formed the first curve on the left side of the heart shadow.

Roentgen-ray examination of the chest revealed the heart shadow to be pushed over to the left by a small effusion in the right pleural cavity. (Fig. 1.) The heart was enlarged and was rotated so that in the anteroposterior position the aortic shadow was not visible. The first curve of the left border of the heart was formed by a markedly dilated and prominent pulmonic artery. The unusual dilatation and pulsation of the pulmonic artery were best seen in the right oblique position. In this plane the left auricle was seen to be extremely dilated and to encroach upon the retrocardiac space. The angle at the bifurcation of the trachea was straightened out. The aortic shadow was barely visible. Both the right and left ventricles were enlarged, but no roentgenographic evidences of pericardial effusion could be made out.

The electrocardiogram revealed good voltage with a right ventricular predominance and auricular fibrillation. (Fig. 2.)

On May 1, 1928, a thoracentesis of the right pleural cavity yielded 1300 c.c. of clear yellowish fluid. Two days later, a similar amount of fluid was removed from the same side of the chest. In performing the second operation the puncture needle was inserted to the inner side of the angle of the right scapula and 40 c.c. of a turbid, dark, yellowish fluid was removed at first which, because of its distinctly different opacity, was thought to have come from the pericardial sac. A second procedure at this time with the needle inserted to the outer side of the right scapula in the seventh intercostal space yielded a clear, straw colored fluid. The cultures of all the fluids were sterile.

The pulsations previously observed in the second and third intercostal spaces became more prominent, each systole resulting in the development of a slight aneurysmal bulge in these intercostal spaces that extended from the left border of

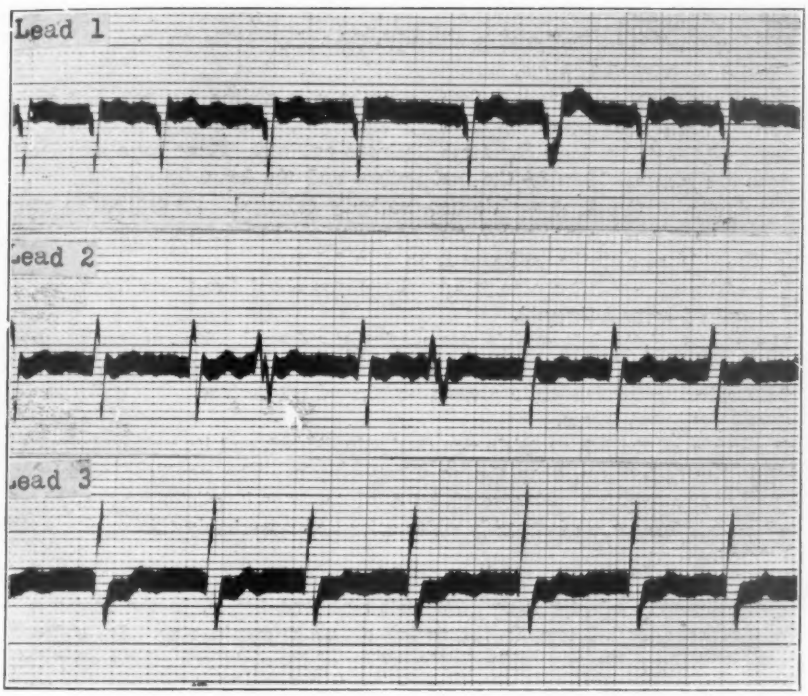

Fig. 2.—The electrocardiogram revealed right ventricular predominance and auricular fibrillation with many aberrant ventricular complexes.

the sternum to the axillary region. The systolic thrill over this region was rougher and more pronounced. Both the systolic and diastolic murmurs heard over this area were now very loud, the former being very rough and the latter softer in quality and occupying all of diastole. Both of these thrills and murmurs were different in quality and character from those audible at the apical region. The heart rate was totally irregular and there was a pulse deficit of 24. The blood pressure was 100/80 mm. There were no peripheral signs of aortic insufficiency such as a Corrigan pulse or capillary pulsation of the fingers.

The x-ray examination of the chest at this time showed signs of pleural effusion at the right base extending up to the fourth rib posteriorly. The heart was markedly enlarged, the left border almost reaching the lateral wall. The right cardiac border was obscured by the overlying shadow. The aorta was not visible

at all in the anteroposterior position. There was an increase in the size of the pulmonic artery as compared with the previous plate.

On May 5, 1928, at about 6 P.M., the patient became very listless and shortly thereafter, comatose. She died at 2 A.M. of that day. A post-mortem pericardial tap at the level of the third intercostal space 4 cm. to the left of the sternum yielded only 40 c.c. of slightly turbid yellowish fluid.

Autopsy Findings.—The autopsy was performed by Dr. Bernard Seligman six and a half hours post-mortem.

A post-mortem radiographic examination of the chest with the body in a sitting posture revealed the presence of small quantities of air in both pleural cavities. The main bulge of the heart extending on the left upper border from the third intercostal space to the clavicle was well defined and recognized as a largely dilated pulmonic artery.

The incision was unfortunately limited so that it was impossible to correlate exactly the position of the heart *in situ* with the radiographic findings.

The heart weighed 600 gm.

The parietal pericardium was free from the surrounding tissues. The visceral surface of the pericardium over the right auricle was thickened and covered for a distance of about 2 × 1 cm. by fresh fibrinous exudate. There were no adhesions between the visceral layer of the pericardium and the heart.

The cavity of the right auricle was markedly enlarged. Its trabeculae carneae were prominent and hypertrophied, and its endocardial surface was smooth throughout. The thickness of the wall was from 1 to 1.5 mm.

The cavity of the left auricular appendage was about five times the normal size and contained several thrombi.

The cavity of the left auricle was markedly enlarged. Its endocardial surface was smooth and glistening but of a grayish color. There were a few small, slightly raised, yellowish white areas near the mitral surface. Its wall was thickened and measured 2 mm.

The cavity of the left ventricle was markedly dilated, and its wall measured 1 cm. at the apex and 2 cm. near the papillary muscle. The papillary muscles were markedly hypertrophied and covered by a white, smooth, glistening surface. The chordae tendineae were of a pearly white color and remarkably thickened, shortened and fused.

The cavity of the right ventricle was tremendously dilated. Its endocardial surface was smooth and glistening. Its wall measured 5 mm. in the region of the pulmonic conus, and 3 mm. in the region of the tricuspid ring. Its endocardial surface near the pulmonary orifice in the region of the right posterior cusp presented a thickened, pearly white area measuring 1 cm. in diameter with a crescentic superior surface appearing as a redundant fold fusing with the under surface of the cusp.

The pulmonic ring was markedly dilated and measured 7.75 cm. (Fig. 3.)

The left posterior and anterior cusps of the pulmonary valve were fused together on their contiguous borders. For a short distance in this region, there were two distinct folds of the valve margins which were not in any way different in consistency from the remainder of the valves. These presented a small triangular depression between them. The two margins of the valve were fused near the insertion of the cusps. The free borders of the cusps were thickened and rolled inwardly but showed no vegetations.

The free border of the right posterior cusp presented almost in its entirety a large, thick firm mass of agglutinated calcified nodules which were contiguous with a similar area of a large and uniformly hardened nodule on the endocardial surface of the right ventricle adjacent to them. On section, these were sclerotic, calcified, grayish yellow in color and extended to the base of the cusp almost obliterating the entire sinus. (Fig. 4.)

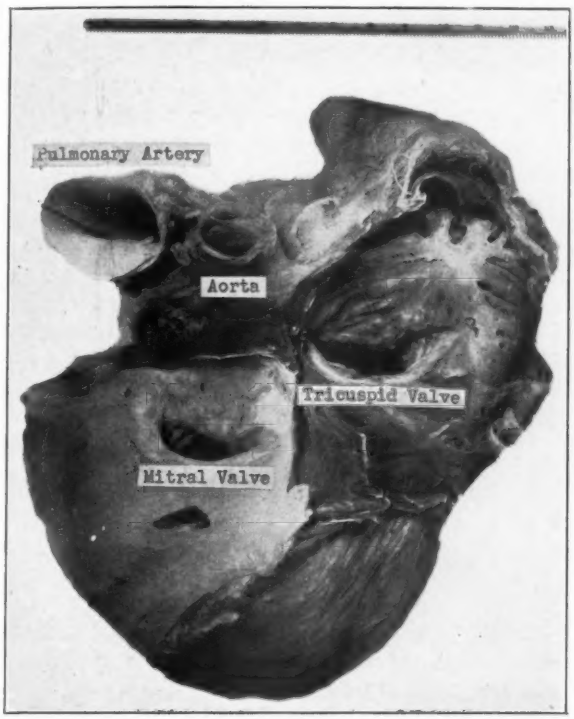

Fig. 3.—The heart shortly after its removal from the thoracic cavity showing the unusual dilatation of the pulmonic artery beyond the pulmonic ring. Compare its diameter with that of the aorta.

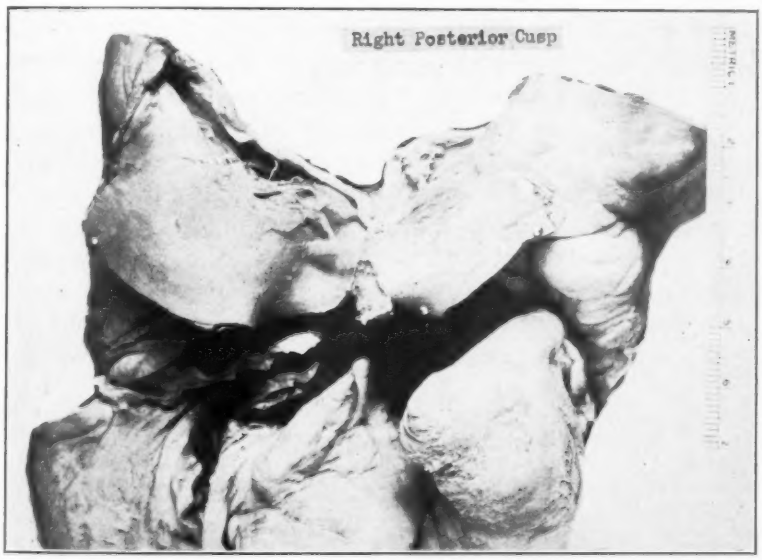

Fig. 4.—The bicuspid pulmonic valve showing rheumatic valvulitis of both valves with inward rolling of the hard firm edges and a large calcified agglutinated mass covering the anterior surface of the right posterior cusp.

The pulmonary artery above the pulmonary valve was wider than the pulmonic ring, measuring in this region 8.75 cm. Its surface presented few small, soft, raised, yellowish plaques.

The mitral valve admitted the tips of two fingers. The free borders of both leaflets were markedly thickened, rolled inwardly and white in color and on the atrial surface showed marked indentations which felt very hard and were sclerotic. Both leaflets presented numerous small fresh vegetations which were conglomerant and in part calcified. Throughout the entire aortic leaflet of the mitral valve, but particularly nearer the mitral ring, there was a small area measuring 2 cm. × 2.5 cm. of a firm calcified mass which was thickened over a distance of about 4.5 cm. In one area the endocardium was denuded and exposed this translucent material. The outer leaflet showed thickening and was pearly white in color.

The tricuspid orifice was moderately dilated. The valves were thin and pearly white in color and the thin free edges were slightly thickened and rolled inwards. The ring measured 10.5 cm.

The aortic ring measured 6 cm. The cusps were well preserved and thin. There were no vegetations present. None of the leaflets were thickened.

The aorta showed a few small, soft, raised, yellowish plaques.

The coronary vessels were slightly thickened and showed raised, diffuse, confluent, small yellowish plaques.

DISCUSSION

The interesting lesion in this patient as revealed by the autopsy findings, in addition to the evident mitral and tricuspid lesions, is an acquired rheumatic valvulitis superimposed on a malformation of the pulmonic valves which in this case consisted of absence of one of the pulmonic leaflets. This underlying congenital malformation may explain the unusual dilatation of the pulmonic artery for so long a period since the first diagnosis of pulmonic insufficiency was made seven years prior to her death; for it is well known that such congenital defects of this artery may produce an insufficiency of the valves even in the absence of any acquired disease.[5] It is very likely, in view of the rarity of acquired rheumatic lesions of the pulmonic artery, that the congenital malformations were responsible in part for the localization of the rheumatic virus on the pulmonic leaflets.

The characteristic roentgen-ray picture of pulmonic insufficiency, as described by one of us[4] in a previous communication, was of great help in the diagnosis of that particular lesion whereas the stenosis of the valves was suspected solely from the clinical evidences which in the main were the rough systolic thrill and localized murmurs in the region of the second intercostal space to the left of the sternum.

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Department of Reviews and Abstracts

Selected Abstracts

Gross, Louis, Antopol, William, and Sacks, Benjamin: A Standardized Procedure Suggested for Microscopic Studies on the Heart. Arch. Path. **10**: 840, 1930.

The authors have developed a procedure for cutting blocks of heart muscle tissue which show a maximum number of lesions in a minimum number of blocks. The six blocks include the four valves, the four valve rings, the pericardium of the left and right sides, the heart, the left and right auricles, the myocardium of the left ventricle, right ventricle, interventricular septum and left posterior papillary muscle; the bases of the aorta and pulmonary artery; the pericardial wedges abutting against the valve rings; the neuromuscular bundle, and the coronary sinus.

It is pointed out that the myocardium in practically every section is taken from a site where the vessels can be considered end vessels. It is probably for this reason that early vascular changes and their results are so frequently observed in these sections, and that inflammatory lesions, which may possibly owe their localization to the fact that the vessels in this region are terminal, are so frequently found here.

By using these sections only, the authors have been able to find Aschoff bodies in 90 per cent of 40 hearts showing acute verrucous endocarditis and in 15 per cent of 39 hearts showing chronic valvular disease. In some of the hearts not showing these lesions, sections from other parts were taken as well, but failed to show Aschoff's bodies.

Middleton, William S., and Oatway, William H.: Insulin Shock and the Myocardium. Am. J. M. Sc. **181**: 39, 1931.

The authors have studied the changes occurring in the heart of 11 patients during insulin shock. They have observed the establishment of common changes in certain of the component waves of the electrocardiogram and to less common but more serious errors in conduction during insulin shock.

Because of the gravity of the changes noted in the presence of myocardial lesions, particular caution is enjoined in the use of insulin in such patients. Where any question exists, the avoidance of hypoglycemia must be insured by an adequate coverage of insulin through concomitant intravenous glucose injections even though there is no agreement as to the causal relationship of the depressed blood sugar.

Hurxthal, Lewis M.; Menard, O. J.; Bogan, M. E.: The Size of the Heart in Goiter. A Teleroentgenographic Study. Am. J. M. Sc. **180**: 772, 1930.

Teleroentgenograms were made on one hundred consecutive cases of toxic and one hundred consecutive cases of nontoxic goiter. No difinite relationship could be found between the duration of the disease or weight loss and the size of the heart. Cardiac enlargement as determined by teleroentgenography showed a fairly direct relationship to age and coincident cardiovascular disease.

The number of enlarged hearts of different degrees was practically the same in both toxic and nontoxic goiter.

The authors conclude that if hyperthyroidism causes cardiac enlargement or hypertrophy and dilatation, it is slight.

Cotton, Thomas F.: The Treatment of Mitral Disease in Children. Brit. M. J. **1:** 481, 1931.

The author has selected the first one hundred boys admitted to a convalescent cardiac home in the years 1919 to 1922 with rheumatic heart disease. The after histories of all but six of these have been obtained after seven years in one group and eight years in another. All have had rheumatism or chorea and all but two have had signs of a rheumatic infection of the heart. Fifty-seven were diagnosed as having mitral disease, twenty-three mitral stenosis, fourteen mitral stenosis and aortic regurgitation and four had aortic regurgitation alone.

The author believes that mitral disease in children is probably always associated with a rheumatic invasion of the myocardium and is evidence of carditis. At the end of seven years, 17 or 29 per cent were dead. Fifteen of those with mitral stenosis or 65 per cent were dead after 8 years. In the smallest group there were 14 cases of mitral stenosis and aortic regurgitation, six of whom were dead after 8 years.

From a study of this group it seems permissible to state that the prognosis in children with mitral stenosis over a period of eight years who have had careful treatment in a special convalescent home is a grave one. They raise the question of this form of treatment in mitral stenosis and whether it is worth while treating such cases in a special convalescent home.

The treatment of children with chronic rheumatism is unsatisfactory when they belong to the poorer classes. On leaving the convalescent home where they have been more or less protected against reinfection they return to unhealthy homes and are again exposed to rheumatic and other infections which cause more damage to the heart muscle and valves. The children of well-to-do persons are better protected against the ravages of rheumatism for they have home surroundings in which they can live, grow up and be educated under conditions which are comparable to those which exist in a special convalescent home. The prognosis is more favorable in these children because the disease is likely to be recognized in its early stages and suitable treatment given at a time when it is possible to prevent the development of progressive changes leading to a serious cardiac disability.

Slater, Solomon R.: The Involvement of the Coronary Arteries in Acute Rheumatic Fever. Am. J. M. Sc. **181:** 203, 1931.

Three cases of adults with acute rheumatic fever are cited in detail which showed electrocardiographic evidence of coronary arterial involvement. The diagnosis of acute coronary closure was also suggested strongly by the symptoms of collapse, pericardial friction rub, leucocytosis and fever. It seemed that in all three cases the endocardium received practically none of the brunt of the attack of the rheumatic virus. All three patients recovered.

It is emphasized that during an acute rheumatic infection any blood vessel, large or small may possibly be involved and that those of the heart may likewise be involved; that when the larger coronary branches are affected under certain circumstances it may be sufficient to encroach so upon the lumen as to occlude it; or a thrombus may occur secondarily producing a closure. When the closure occurs, the patients experience excruciating pains indicative of the lesion.

Parsonnet, Aaron E., and Hyman, Albert S.: Heart Sound Failure. A Phonocardiographic Study of This Phenomenon in Acute Coronary Occlusion. J. A. M. A. **96**: 1124, 1931.

In a series of fourteen cases of acute coronary thrombosis in which heart sound failure had been a conspicuous feature, graphic methods of study have been employed. In eleven of these there have been uniform phonocardiographic alterations in the sounds. The authors believe that heart sound failure may be regarded as one of the pathognomonic signs of coronary thrombosis and when the diagnosis is rendered uncertain by the predominance of symptoms apparently arising from other sources, the discovery and recognition of this characteristic impairment of tone quality may go far to clear up the problem at hand.

Proger, Samuel H.: The Electrocardiogram in Obesity. Arch. Int. Med. **47**: 64, 1931.

The electrocardiogram of the obese person with an apparently normal heart in a large percentage of cases shows left axis deviation, flattening or inversion of the P-wave; inversion of T-wave in Lead III. In those cases in which the heart appears to be normal there are no significant changes in the T-wave in Leads I and II, regardless of the extent of the axis deviation. Left axis deviation due to change in position is usually associated with inversion of the T-wave in Lead III, whereas left axis deviation owing to relative left ventricular hypertrophy is commonly associated with an erect T-wave in Lead III.

Cases of obesity without other organic disease show approximately the same incidence and extent of left axis deviation as cases of obesity complicated by hypertension and cardiac enlargement. Axis deviation in electrocardiogram of the obese patient is of no value as an aid in the diagnosis of relative ventricular hypertrophy.

There appears to be a general relationship between the anatomic angle of the heart as measured on the orthodiagram and the electrical angle as calculated from the electrocardiogram.

Factors such as age, sex, duration and percentage of overweight beyond 25 per cent seem to have no definite relation to changes in the electrocardiogram.

Hill, Ian G. W.: Bundle Branch Block. Quart. J. Med. **23**: 15, 1930.

Forty-one cases of bundle branch block with clinical findings are recorded. A diagnosis of this condition by means of physical signs alone is not feasible. No demonstrable change in the ventricular complexes could be produced by therapeutic doses of atropin and digitalis.

The right branch of the bundle was traced by serial sections in two cases which during life showed the features of right bundle branch block. In both, and in one child's heart cut as a control the right branch was formed to split up or lose its identity at a higher level than was expected from anatomical teaching. In one case in addition to widespread fibrosis of the myocardium which did not involve the bundle or its branches foci of round celled infiltration were demonstrated in the main stem and in the right branch. From their nature and from the known syphilitic element in the case, these foci are thought to be possibly of a specific origin.

The question of "incomplete bundle branch block" has been considered and it is urged that this term be not applied to cases yielding an incomplete electrocardiographic picture of bundle branch block but solely to cases which show analogy to incomplete block of the main stem, i.e., delayed conduction.

Beresford, E. H., and Earl, C. J. C.: Spontaneous Cardiac Rupture. A Review of Forty-Six Cases. Quart. J. Med. **23**: 55, 1930.

Forty-six cases of spontaneous cardiac rupture are reviewed and discussed. Recent acute infarction of the heart is considered to be almost invariably the underlying cause.

The incidence in this group increased with advancing years, the highest figure being reached in the eighth decade. In this group of cases after making allowances for errors in grouping, the cases occurred in the ratio of about four females to one man. This opposes the view determined from previous similar series of cases. The frequent association of insanity with cardiac rupture is remarkable.

Mechanism of the rupture is discussed and the importance of excessive fat, of softening and of hemorrhage as factors is emphasized.

Stewart, Sloan G.: Problems of Cardiac Disease Associated with Urinary Retention. Am. J. M. Sc. **181**: 362, 1931.

There is a group of cases in which lower urinary tract obstruction and evidences of cardiac disease are commonly associated. That this may be of primary importance, from a therapeutic standpoint, is illustrated by clinical reports of two cases. The need of adequate urological histories and examinations in the medical studies on all male patients is emphasized. A brief statistical review of forty cardiac cases with prostatic obstruction reveals cardiac arrhythmias in a large percentage of cases and widespread arteriosclerosis and coronary sclerosis of an unusually advanced type. Two cases are reported of myocardial failure refractory to rest and digitalis in which bladder retention without obstruction was discovered. The results of constant bladder drainage as a therapeutic measure are discussed. The determination of prognosis of these cases and the evaluation of infection as a complication of catheter drainage are difficult problems which are briefly presented.

Andersen, Maine C.: Paroxysmal Ventricular Tachycardia. Am. J. M. Sc. **181**: 369, 1931.

A case of paroxysmal ventricular tachycardia in which there was no evidence of serious heart disease is reported with electrocardiographic records. The author believes that the slight displacement in the auriculoventricular rhythm in paroxysmal ventricular tachycardia is sufficient to cause the cyclic accentuation of the first sound at the apex.

It is suggested that in paroxysmal ventricular tachycardia occurring in an individual—not the subject of demonstrable heart disease—there is not only an inherited sensitive nervous system but also an inherited cardiac neuromuscular aberration.

Parkinson, John, and Campbell, Maurice: Paroxysmal Auricular Fibrillation. Quart. J. Med. **23**: 67, 1930.

This paper is based on the notes of 200 patients who had paroxysms of auricular fibrillation. It is believed that the cases can be divided into three groups; one, typical recurrent paroxysms which form more than one-half of the cases in this group; two, a few paroxysms preceding the onset of established fibrillation; three, single or very occasional paroxysms often of longer duration seen in the case of congestive heart failure, after coronary thrombosis, with infections such as pneumonia or with no apparent cause.

During the immediate attack, the prognosis is excellent but if the attack lasts more than several days permanent fibrillation becomes much more likely and after

two weeks is almost certain. Seventy per cent of the cases studied showed signs of structural heart disease. The symptoms usually were not severe. With a longer attack or where the heart was already in difficulty all the signs and symptoms of congestive heart failure were seen.

Master, Arthur M.: Low Voltage T-Waves in the Electrocardiogram. Am. J. M. Sc. **181**: 211, 1931.

In 107 patients a study was made of low voltage T-waves in which the amplitude in any lead was not more than 1 mm. In 12 patients that were examined post-mortem all showed definite myocardial or pericardial damage. Another group of 12 patients died but no autopsy was performed. Eleven died with typical myocardial failure and 1 of pulmonary tuberculosis.

Altogether, there were 89 hospital patients with flat T-waves, the mortality among those with degenerative cardiovascular disease was at least 44 per cent during the course of a three to four years' investigation.

Acute rheumatic infection of the myocardium or pericardium often produces a flat T-wave and in the progression of the disease the T-wave may become inverted or if the patient recovers, it will become upright. The rheumatic cardiac patient with a flat T-wave is acutely ill and is probably always a bed patient. The so-called coronary T-wave or cove-plane T-wave that is customarily associated with coronary artery occlusion may appear in a patient with rheumatic pericarditis. Suggestive evidence is presented that pericarditis alone without disease of the underlying myocardium, may cause a flat T-wave. When a flat T-wave appears in the course of other diseases it seems to indicate a very severe form of illness. These T-waves are practically always transitory becoming inverted as the myocardial or pericardial damage spreads and increasing in amplitude on cure or improvement.

Parkinson, John, and Bedford, D. Evan: Electrocardiographic Changes During Brief Attacks of Angina Pectoris. Lancet **1**: 15, 1931.

In 5 patients with attacks of angina pectoris electrocardiograms taken during short paroxysms show definite and transitory changes in the ventricular deflections. There was a depression of R-T and a diminution in the amplitude or inversion of the T-waves in one or more leads, changes closely resembling though not so pronounced as those which follow cardiac infarction in the early stages. It is surely significant that both transient anginal pain and cardiac infarction can affect the electrocardiogram in a similar manner; and it seems reasonable to infer that the mechanism underlying this electrocardiographic change is essentially the same in both cases—an ischemia of a part of the cardiac muscle.

The authors do not suppose that the electrocardiogram is always modified during short anginal attacks but their evidence suggests that it is modified in a proportion of cases.

Levy, Robert L.: Mild Forms of Coronary Thrombosis. Arch. Int. Med. **47**: 1, 1931.

A group of eight cases is reported as exemplifying mild forms of coronary thrombosis. The records of these patients appear to define a distinct clinical group characterized by the relative youth of the patients and rapid rate of recovery both subjective and objective. One of the eight patients died of a second attack; one patient had a second occlusion one year after the first; another has had two later attacks; restoration of function has been complete in two patients; two of the patients are free from symptoms on restricted activity; three have symptoms even with carefully regulated lives; two still complain of pain in the heart and one of dyspnea on effort.

It is believed that this condition frequently is not recognized because of the atypical clinical picture. Although a rapid rate of recovery tends to indicate a favorable outcome of the immediate attack, accurate prognosis as to the liability to recurrence and life expectancy is extremely difficult.

Wood, Francis C., and Wolferth, Charles C.: Angina Pectoris. The Clinical and Electrocardiographic Phenomena of the Attack and Their Comparison with the Effects of Experimental Temporary Coronary Occlusion. Arch. Int. Med. **47**: 339, 1931.

Thirty cases of angina pectoris were studied electrocardiographically before, during and after their attacks. Fifteen showed temporary ventricular complex changes during the pain, which probably cannot be explained by the exercise which produced the attacks nor by the changes in blood pressure and pulse rate which accompanied them. The remaining fifteen showed no specific electrocardiographic changes during their attacks. The severity of the pain did not seem to be the main factor that determined the presence or absence of "specific" electrocardiographic change during an attack. The relief of anginal pain by nitrites does not always seem to be dependent on the drop of blood pressure which this group of drugs produces. The prognostic importance of specific electrocardiographic changes during attacks has not as yet been determined. Although there were no untoward occurrences in this series of cases, the authors are not prepared to recommend the electrocardiographic procedure described as a diagnostic test in angina pectoris.

In a series of dogs and cats temporary interference with a part of coronary occlusion produced temporary and rapidly reversible changes in the electrocardiogram somewhat analogous to those seen during attacks of angina pectoris.

The factors that seem of importance in the production of these changes were: (1) the vessel that was occluded; (2) the size of the area of the myocardium the blood supply of which was interrupted; (3) the state of the heart before the vascular occlusion; (4) the duration of the occlusion and (5) possibly the simultaneous obstruction of accompanying veins.

Experimental temporary coronary occlusion frequently produced no electrocardiographic change, therefore the absence of specific electrocardiographic change in fifteen patients during attacks of angina pectoris cannot be used as evidence that temporary myocardial ischemia did not occur. In experimental coronary occlusion, cardiac arrhythmia which could be attributed to the circulatory disturbance in itself was not a frequent early phenomenon. When it did occur it seemed to be attributable to mechanical stimulation of the heart muscle by the mechanism producing the occlusion.

The evidence presented is in accord with the hypothesis that the majority of attacks of angina pectoris are associated with a localized circulatory disturbance of the heart. It does not rule out the possibility that other mechanisms may produce paroxysms of precordial or substernal pain.

Findlay, Leonard, MacFarlane, James W., and Stevenson, Mary M.: Rheumatic Pericarditis in Childhood. Arch. Dis. Child. **5**: 1, 1930.

The authors have studied the records of 51 examples of rheumatic pericarditis admitted to the Royal Hospital for Sick Children, Glasgow, between 1915 and 1928 inclusive. Of thirty post-mortem examinations in children dying from all forms of rheumatic heart disease, there were implications of involvement in the pericardium in 50 per cent. In two of the cases pericarditis apparently was the sole cardiac lesion, 44 of the 51 patients had suffered at some time or another from arthritis,

15 of the patients had suffered from chorea but 13 of them had also had arthritis so that in only 2 children was chorea the sole other rheumatic manifestation than the cardiac involvement. Thirty-two cases were females and 19 males. Of the 51 cases 26 died, 24 during acute phase of the disease and 2 at a later date from cardiac decompensation. Of the 25 cases still alive, there was one with neither signs nor symptoms of cardiac disease; in 7 cases there are signs of cardiac disease but no symptoms; in 9 there are definite symptoms of cardiac disability as well as signs and in 3 the disability is extreme.

Sutton, Lucy Porter: Pericarditis with Effusion. Am. J. Dis. Child. **41**: 78, 1931.

The object of this paper is to call attention to the pulmonary signs associated with moderate and large pericardial effusion. Several cases are reported together with x-ray illustrations and charts describing the signs.

The posterior site for tapping the pericardium is described. It is believed to be perfectly safe and one is far more certain of reaching the fluid than in using the points formerly recommended. Although only one of these cases seemed to require relief because of the size of the effusion, it appears possible that removal of some of the fluid may hasten absorption and thus lead to quicker recovery.

Wood, Francis C., and Eliason E. L.: Rheumatic Peritonitis. Am. J. M. Sc. **181**: 482, 1931.

A patient with a past rheumatic history and a well-marked rheumatic cardiac lesion developed lower abdominal pain, diarrhea and signs of peritoneal irritation. Operation disclosed an abundance of clear fluid in the peritoneal cavity and an acute serositis and subserositis of the peritoneum of unknown etiology. Nine days after operation acute pericarditis developed and after a stormy course of typical cardiac rheumatism of six weeks' duration the patient died.

It seems worth while to bear in mind the possibility of rheumatic peritonitis in the differential diagnosis of abdominal pain where it occurs in a patient with signs of present or past rheumatic fever.

Scott, L. C.: The Potassium Content of the Hearts of Persons Dying from Edematous and Nonedematous Conditions. Arch. Int. Med. **47**: 116, 1931.

In a series of 69 analyses of cardiac muscle for inorganic constituents special attention was paid to the potassium and sodium in 32 hearts from patients who had died from a variety of diseases. Fourteen of these patients showed edema of a greater or lesser degree and of varying periods of duration and eighteen were free from it. The results do not seem to indicate that there is on an average any appreciable difference in the amount of these elements in hearts from edematous and from nonedematous patients.

There is considerable variation in the amount of potassium and sodium in hearts regardless of whether the disease processes from which the patients died were or were not productive of edema. The percentage of sodium may be greater than that of potassium and vice versa without any apparent relation to disease.

Demonstration of potassium in cardiac tissue by Macallum's sodium cobaltrinitrite method indicates that the larger proportion of the salts is contained in the fluid bathing the muscle cells, and that they are rather uniformly diffused throughout the protoplasm.

Calhoun, J. Alfred, Cullen, Glenn E., Clarke, Gurney, and Harrison, T. R.: Studies in Congestive Heart Failure. VI. The Effect of Overwork and Other Factors on the Potassium Content of the Cardiac Muscle. J. Clin. Investigation **9**: 393, 1930.

The water content of the ventricular muscles of subjects dying of congestive heart failure was not significantly increased. Patients dying with acute and extensive disease of the lungs had diminished potassium content of the right ventricle but not of the left ventricle. When myocardial insufficiency results in pulmonary congestion, the potassium content of the left ventricle is diminished. When myocardial insufficiency results in hepatic and systemic edema, the potassium content of the right ventricle is decreased. If both systemic and pulmonary congestion were present, both ventricles were poor in potassium. The cardiac potassium was not diminished in a subject with concretio cordis and myocardial atrophy. The dilated ventricles were poor in potassium; the ventricles which were hypertrophied but not dilated showed variable results.

The authors believe that edema is not the cause of loss of cardiac potassium; they believe that overwork causes loss of potassium from heart muscle and this loss is one of the predisposing factors to cardiac fatigue and failure.

Calhoun, J. Alfred, Cullen, Glenn E., and Harrison, T. R.: Studies in Congestive Heart Failure. VII. The Effect of Overwork on the Potassium Content of Skeletal Muscle. J. Clin. Investigation **9**: 405, 1931.

Overwork of the muscles of one leg in dogs produced by stimulation of the sciatic nerve usually leads to a diminished content of potassium in these muscles as compared with those of the opposite unstimulated leg.

Calhoun, J. Alfred, Cullen, Glenn E., Clarke, Gurney, and Harrison, T. R.: Studies in Congestive Heart Failure. VIII. The Effect of the Administration of Dibasic Potassium Phosphate on the Potassium Content of Certain Tissues. J. Clin. Investigation **9**: 693, 1931.

The total solid and potassium content of skeletal muscle, of cardiac muscle from both ventricles and of liver and kidney have been determined in subjects dying without cardiac disease; individuals dying of congestive cardiac failure, who did not receive potassium salts, and patients dying of congestive cardiac failure who were given potassium dibasic phosphate during life. All the subjects with cardiac disease had had edema, although some of them had none at the time of death.

The organs of the "control" cases contained, as an average, more potassium in both the wet and dry tissues than was found in the subjects with cardiac disease.

Among the subjects with cardiac disease, the average content of tissue potassium was greater in the subjects who received the potassium salt than in those who did not. The difference was most striking in the skeletal muscle and least marked in the heart.

Eyster, J. A. E., and Meek, Walter J.: Studies on Venous Pressure. Am. J. Physiol. **95**: 294, 1930.

Venous pressure in the dog under anesthesia tends to show relatively small and transitory changes under conditions which alter markedly the physical conditions existing in the cardiovascular system. There appear to be compensatory factors present tending to prevent excessive changes and to cause rapid restoration to a normal level.

There appears to be little if any direct relation between arterial pressure and the pressures in different parts of the venous system. Inverse changes occur as frequently as direct, and both may be present simultaneously if different parts of the venous system are considered.

In general the pressure is more stable and less subject to alteration in the peripheral veins than in the right auricle. There appears to be some factor or factors tending to reduce the extent of change arising at the heart as measured further out in the vascular system. Not infrequently inverse changes may occur in the periphery as compared with the auricular pressure change, but in all cases the result is transitory and rapid readjustment occurs.

These results tend to emphasize the fact that the vascular system particularly the venous part cannot be reduplicated physically by a simple hydraulic model. Many factors, some unknown and some only partially recognized, modify markedly the comparison to a more or less static system of channels. Two of these factors, the varying response of the heart to varying venous loads and the variable capacity of the vascular bed, would seem to be of essential importance.

Stewart, Harold J., and Moore, Norman S.: The Number of Formed Elements in the Urinary Sediment of Patients Suffering from Heart Disease, With Particular Reference to the State of Heart Failure. Jour. Clin. Investig. **9**: 409, 1930.

The present study is concerned with the estimation of the number of formed elements in the urine of patients suffering from chronic heart disease, especially in the so-called arteriosclerotic type more particularly with reference to the state of heart failure of the congestive type.

The most consistent finding was increase in the number of casts, the average being 20 to 60 times greater than normal, depending on the severity of the disease. The number was smallest when failure of the congestive type had not occurred, somewhat greater when it had, though at the moment no signs were present and greater still when they were.

During heart failure and after recovery increased numbers of red and white blood cells occur almost so frequently they are within the normal range.

Moon, V. H., and Stewart, H. L.: Experimental Rheumatic Lesions in Dogs and in Rabbits. Arch. Path. **11**: 190, 1931.

While conducting experiments on chronic focal infections with streptococci, results were obtained that are of interest because of their bearing on the pathogenesis of rheumatic fever. Young dogs and rabbits not subjected to sensitization or other previous treatment were inoculated with Streptococcus viridans from a case of bacterial endocarditis in man. The manifestations of disease which followed were very similar to the clinical features of acute rheumatic fever. The gross and microscopic lesions in these animals were identical with those that characterize rheumatic disease. The organism inoculated was recultivated from some of the lesions and was demonstrated microscopically in sections from others.

These results followed a combination of intravenous inoculation with implantation of chronic focus. The authors maintain that this mode of inoculation is not essential to production of the lesions. They believe the use of young animals and of freshly isolated cultures was of great importance in producing the lesions described. These results strengthened the evidence that streptococci of low virulence are the direct cause of rheumatic disease.

Gordon, Harry, and Perla, David: Subacute Bacterial Endarteritis of Pulmonary Artery Associated with Patent Ductus Arteriosus and Pulmonic Stenosis. Am. J. Dis. Child. **41**: 98, 1931.

An incidence is reported of subacute bacterial endarteritis of the pulmonary artery associated with a patent ductus arteriosus and a congenital pulmonary stenosis; none of the valves were involved. The relationship of congenital defect to bacterial inflammation is discussed. The group of cases analyzed suggests strongly the importance of mechanical stress.

Richards, Dickinson W., Riley, Constance B., and Hiscock, Mabelle: Congenital Heart Disease. Measurements of the Circulation. Arch. Int. Med. **47**: 484, 1931.

Clinical, physiologic and pathologic studies have been made in a case of congenital malformation of the heart, the anatomic lesions of which were those forming the tetralogy of Fallot combined with a patent ductus arteriosus. The course of the circulation is described and illustrated by a chart.

From the point of view of experimental method this study has been of especial interest in that the technic employed is shown to have given fairly accurate results with at least one type of pathologic circulation.

Saphir, Otto: Endocardial Pockets. Am. J. Path. **6**: 733, 1930.

In two cases of subacute bacterial endocarditis of the aortic and mitral valves with insufficiency of the aortic valve, endocardial pockets with openings toward the aorta were found on the interventricular septum of the left ventricle. The initial lesion which brought about the pocket formation was a circumscribed parietal endocarditis. The continuous regurgitation formed the pockets secondarily.

In one case of rheumatic endocarditis of the mitral valve with insufficiency of this valve, endocardial pockets were present in the left auricle. These pockets were open toward the mitral valve. They also were primarily inflammatory in origin and formed secondarily by the regurgitation after the insufficiency of the mitral valve had been established.

In two cases of syphilitic involvement of the aortic valve with insufficiency of this valve, endocardial pockets open toward the aorta were found. These pockets were caused primarily by the mechanical irritation of the regurgitating blood columns.

Two cases of syphilitic involvement of the aortic valve with insufficiency of this valve and marked stenosis of the conus arteriosus sinister, and one case of rheumatic endocarditis of the aortic valve with stenosis of its orifice, showed endocardial pockets on the interventricular surface of the left ventricle. These pockets were open toward the apex of the heart. They were brought about by the mechanical irritation of the systolic blood stream acting as a trauma upon the endocardium in the region of the stenosed portions.

From these observations it is concluded that diastolic endocardial pockets are evidence in favor of the view of actual regurgitation of blood volume.

The nomenclature of "diastolic pockets" referring to those open toward the aorta and "systolic pockets" referring to those open toward the apex (Krasso) is justified.

Endocardial pockets cannot be regarded as manifestations of functional adaptation.

Taussig, Helen B.: On the Boundaries of the Sino-Auricular Node and the Atrio-Ventricular Node in the Human Heart. Bull. Johns Hopkins Hosp. **48**: 162, 1931.

Blocks of tissue from human hearts were sectioned and the cellular morphology of the S-A and A-V node were studied. It was possible to recognize the limits of these two nodes.

The study shows that in the human heart in certain places at the margin of the A-V node one can trace a gradual transition from the A-V nodal tissue to the auricular cardiac muscle. It was shown that the specialized tissue cells at the outer margin of the sino-auricular node are larger than those in the center of the node also there are purkinge cells extending from the S-A node into the outer wall of the superior vena cava. There are calls closely resembling specialized tissue cells extending from the S-A node into the folds of the auricular musculature. Extensive literature is appended.

Schmitz, Herbert W.: Urobilinuria in Children with Rheumatic Heart Disease. Am. J. M. Sc. **181**: 392, 1931.

This study was concerned with the urinary urobilin estimations on children with rheumatic heart disease during different stages of the disease. Determinations were made on 57 ambulatory cases, 4 cases with recurrent rheumatic carditis without congestive failure and 10 cases of congestive heart failure.

Children with recurrent infection of the heart, but with no evidence of congestive failure may show normal values for the urobilin excretion in a twenty-four-hour period. High values for the urinary urobilin may be observed in children with congestive heart failure, but a high urobilinuria is not necessarily present in these cases, nor does a hyperurobilinuria in children with rheumatic heart disease always mean congestive failure. The urobilinuria does not bear a consistent relationship to the degree of congestive failure and, therefore, cannot be considered a reliable index of the functional efficiency of the heart. It is of no significant value in the diagnosis of the degree of damage, prognosis or the management of the cardiac child.

Bland, Edward F., Balboni, Gerardo M., and White, Paul D.: Enormous Increase of Heart Volume with Mitral Stenosis. J. A. M. A. **96**: 840, 1931.

A young man with mitral disease under observation for nineteen years lived a relatively active life up to the time of his sudden death in spite of an extraordinary amount of cardiac enlargement and an extreme degree of auricular dilatation.

The volume of the filled heart was 4600 c.c., which is from six to seven times that of a normal sized heart and establishes a record for future comparison. In the case recorded cardiac hypertrophy was far less a factor than dilatation in causing the extreme enlargement; the weight was 850 grams, which has often been exceeded. The left auricle had a capacity of 1760 c.c., a measurement exceeded by only three other cases in the literature. The right auricle held 650 c.c. which appears to be a record capacity.

The authors found the literature to be notably deficient in measurements of heart volume. A determination that should be a helpful indication of the degree of responsibility of cardiac dilatation in the production of cardiac enlargement.

New England Heart Association

Sprague, Howard B.: Auscultation and Heart Sounds.
Reid, William D.: Heart Murmurs in the Practice of Medicine.

McCrudden, Francis H.: Heart Murmurs and Insurance.
Weiss, Soma: The Normal Arterial Blood Pressure and Its Measurement.
Palmer, Robert Sterling: Abnormal Blood Pressure.
O'Hare, James P.: Treatment of Hypertension.
New England J. Med. **204**: 583, 1931.

These abstracts represent papers presented at the annual meeting of this association. In abstract form, they discuss the various subjects briefly. These subjects are of general interest and the material presented is clear and much to the point.

Book Reviews

ARTERIAL HYPERTENSION. By Edward J. Stieglitz, M.S., M.D., Assistant Clinical Professor of Medicine, Rush Medical College, University of Chicago. New York, 1930, 180 pages, with illustrations, Paul B. Hoeber, Inc.

The purpose of Stieglitz' book is to give us "the logic of physiologic mechanism" of arterial hypertension so that it may be used at the bedside. He has boldly outlined a theory of the mode of production and maintenance of elevated blood pressures that has the advantage of the simplicity inherent in all unitarian doctrines. Two paragraphs quoted from pages 41 and 44 may possibly give the drift of his argument:

"A fundamental conception to be kept in mind, therefore, is that hypertension essentially results from vascular muscular hypertonia and that when the term 'vascular disease with hypertension' is used it signifies this hypertonia and its subsequent anatomic changes."

"The continuous spasticity therefore leads first to hypertrophy, then to fatigue and finally to hyperirritability, and of course to a further increase in the arterial muscular spasticity. Thus a vicious circle is set in operation. The continuation of the cycle of spasticity, fatigue, hyperirritability, more spasticity, fatigue, etc., is the second of the fundamental etiologic or physiologic phenomena and can well be called 'the perpetuating process of hypertension' in contrast to the 'initiating' process already discussed."

The subject has been presented with a great deal of enthusiasm and the book should appeal to all the lovers of progressive medical thought. The main contentions are, of course, based largely on theory, and the original will have to be studied if it is desired to obtain the spirit of the presentation. Stieglitz stresses the good effects of bismuth subnitrate and of bromides in the treatment of hypertensive states; he is the originator of the idea that the slow liberation of nitrites from bismuth subnitrate in the intestinal canal serves to keep the spastic arterioles in a relaxed state. There are some rather radical statements such as the idea that iodide therapy in arterial disease is grossly illogical and is actually contraindicated because the effect of iodine is one of destruction and weakening of the supporting scaffolding which is being placed about the tottering vascular walls; that the urinary specific gravity with renal decompensation is from 1.002 to 1.006; that

the renal tubules do not reabsorb sugar from glomerular urine but cause it to disappear by utilizing it and many others. Such ideas are teeming with interest and they should form starting points for new ways of thinking that may break the trail for advance in clinical medicine.

H. O. M.